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EXFOLIATIVE-CELL DIAGNOSIS OF CENTRAL NERVOUS SYSTEM LESIONS

WILLIAM R. PLATT, M.D.
CAMDEN, N. J.

IN RECENT years the exfoliative-cell diagnosis of neoplasms having a free surface has been advocated by Papanicolaou [1] and others,[2] using the fixed-smear technique. This method has been utilized in the detection of uterine and cervical carcinoma by examination of the vaginal and cervical smears; in the diagnosis of carcinoma of the laryngo-tracheo-broncho-pulmonary tree by cytologic study of sputum and bronchial secretions; in the diagnosis of malignant changes in the esophageal-gastric-pancreatic-biliary tract by analysis of aspirated gastric-duodenal-biliary contents; in the detection of renal, vesical, and prostatic carcinoma by the study of urethral and bladder urine and prostatic-secretion smears; in the diagnosis of primary and metastatic neoplasms of the pleural and peritoneal cavities by a study

From the Department of Pathology of the University of Louisville School of Medicine and the Norton Memorial Infirmary, Louisville.

Now associated with the Department of Pathology of the University of Pennsylvania School of Medicine and the West Jersey Hospital, Camden, N. J.

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2. Morrison, L. F.; Hopp, E. S., and Wu, R.: Diagnosis of Malignancy of the Nasopharynx: Cytological Studies of the Smear Technique, Ann. Otol. Rhin. & Laryng. **58**:18-32, 1949. Fitz-Hugh, B. S.; Moon, C. N., Jr., and Lupton, C. H., Jr.: Cytological Smear Technique in the Diagnosis of Carcinoma of the Maxillary Sinus, Laryngoscope **60**:376-387, 1950. Jacobson, B. D.: Early Diagnosis of Carcinoma of the Breast by Cytologic Technique, J. M. Soc. New Jersey **47**:337-338, 1950. Woolner, L. B., and McDonald, J. R.: Diagnosis of Carcinoma of Lungs: The Value of Cytologic Study of Sputum and Bronchial Secretions, J. A. M. A. **139**:497-502 (Feb. 19) 1949. Andersen, H. A.; McDonald, J. R., and Olsen, D. M.: Cytologic Diagnosis of Malignant Lesions of Esophagus and Cardia of Stomach, Minnesota Med. **32**:1181-1185, 1949. Pollard, H. M.; Bryant, H. C.; Block, M., and Hall, W. C.: Diagnosis of Gastric Neoplasms by Cytologic Examination of Gastric Secretions, J. A. M. A. **139**:71-74 (Jan. 8) 1949. Lemon, H. M., and Byrnes, W. W.: Cancer of the Biliary Tract and Pancreas: Diagnosis from Cytology of Duodenal Aspirations, ibid. **141**:254-257 (Sept. 24) 1949. Foot, N. C., and Papanicolaou, G. N.: Early Renal Carcinoma in Situ: Detected by Means of Smears of Fixed Urinary Sediment, ibid. **139**:356-358 (Feb. 5) 1949. Chute, R., and Williams, D. W.: Experiences with Stained Smears of Cells Exfoliated in Urine in Diagnosis of Cancer in Genito-Urinary Tract: Preliminary Report, J. Urol. **59**:604-613, 1948. Albers, D. D.; McDonald, J. R., and Thompson, G. J.: Carcinoma Cells in Prostatic Secretions, J. A. M. A. **139**:299-303 (Jan. 29) 1949. Wisseman, C. L., Jr.; Lemon, H. M., and Lawrence, K. B.: Cytologic Diagnosis of Cancer of Descending Colon and Rectum, Surg., Gynec. & Obst. **89**:24-30, 1949. Phillips, S. K., and McDonald, J. R.: An Evaluation of Various Examinations Performed on Serous Fluids, Am. J. M. Sc. **216**:121-128, 1948.

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EXFOLIATIVE-CELL DIAGNOSIS OF CENTRAL NERVOUS SYSTEM LESIONS

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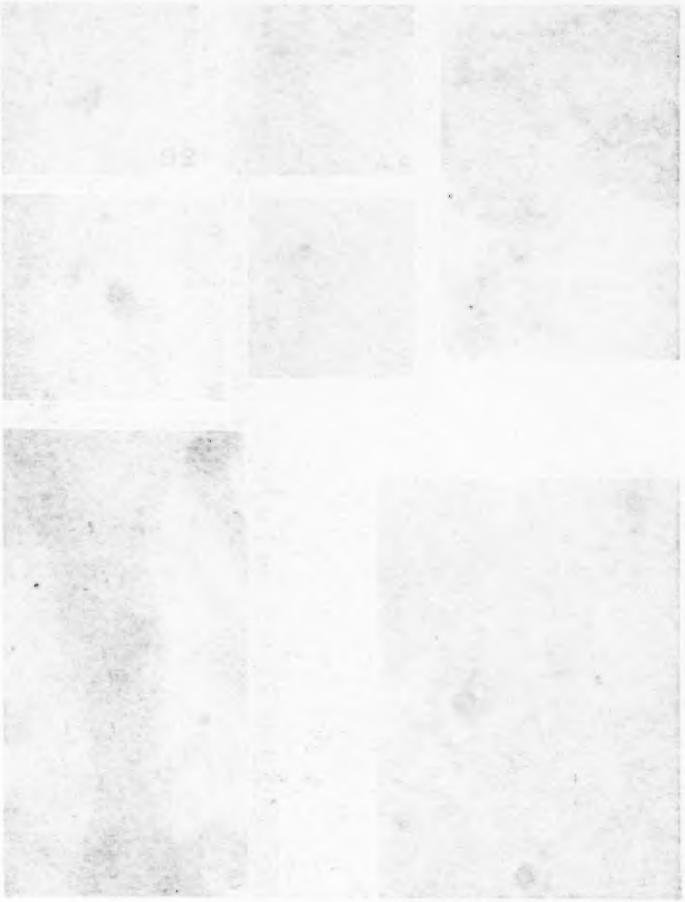
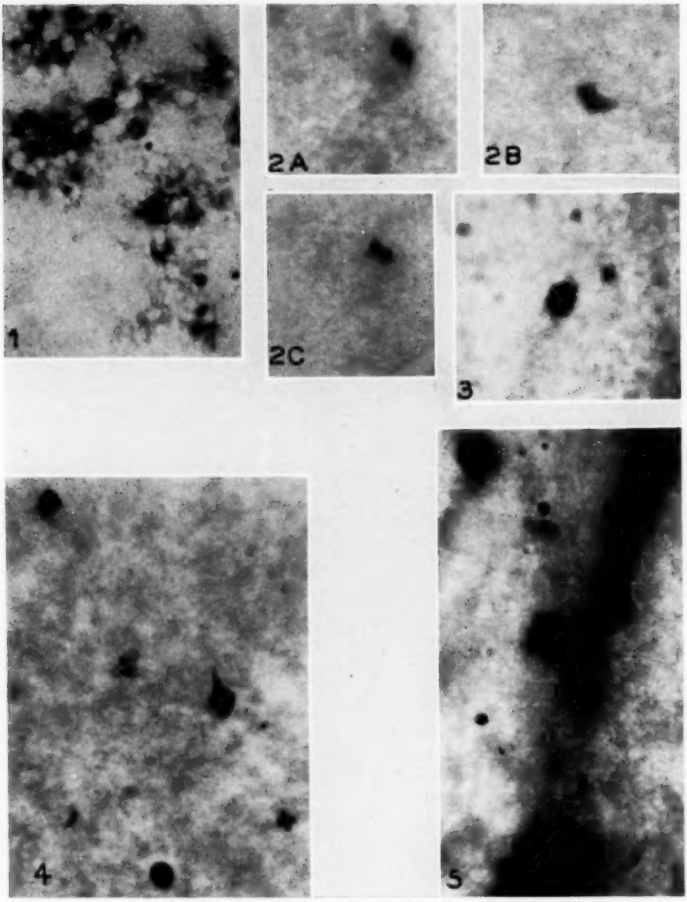
Cleveland, Ohio





Figs. 1-5—*1* (Case 1), ventricular fluid, relatively normal in type, showing lymphocytes, endothelial cells, and cellular detritus. × 430; Papanicolaou stain.

2 (Case 2), nasal fluid in a case of rhinorrhea of cerebral origin, revealing several fields represented by (*A*) endothelial, (*B*) epithelial, and (*C*) juvenile cells. × 430; Papanicolaou stain.

3 (Case 2), ventricular fluid, showing a mononuclear cell, probably a monocyte. × 970; Papanicolaou stain.

4 (Case 2), spinal fluid, demonstrating lymphocytes, cellular detritus, and an endothelial cell. × 430; Papanicolaou stain.

5 (Case 3), fluid from left ventricle, with several lymphocytes and a monocyte. × 970; Papanicolaou stain.

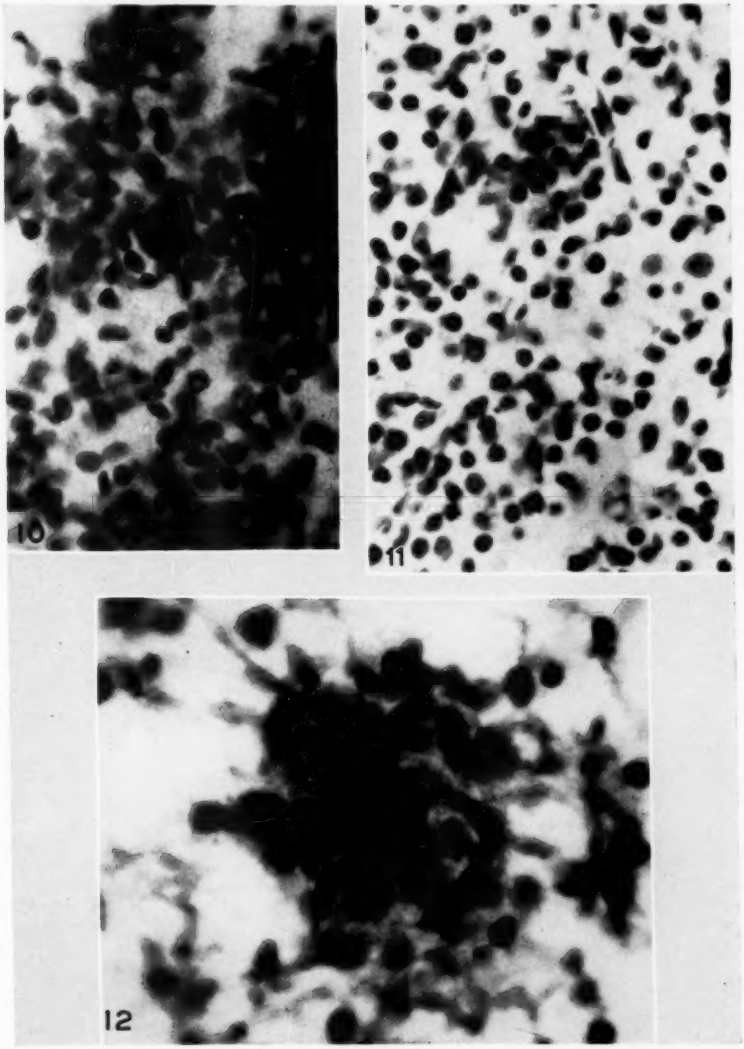
normal condition except for moderate edema of the left orbit. Laboratory examination of the nasal fluid on May 20, 1948, showed a clear fluid with a specific gravity of 1.009 (normal range of specific gravity for lumbar fluid, 1.005 to 1.009; normal range of specific gravity for ventricular fluid, 1.002 to 1.004[7]); the total-protein content was 75 mg. per 100 cc. (total protein of normal spinal fluid for adults, 15 to 45 mg. per 100 cc.); microscopic examination showed an occasional endothelial and epithelial cell (Fig. 2*A*, *B*, and *C*). The plasma, examined on May 21, showed a specific gravity of 1.028 and a total-protein content of 7.2 mg. per 100 cc. The ventricular fluid (specific gravity, 1.004), examined on May 21, revealed a clear, fairly acellular fluid (Fig. 3), containing an occasional lymphocyte and monocyte—Class-I smear. The nasal fluid on May 25 was clear and colorless, with 2 lymphocytes per cubic millimeter and a sugar content of 72 mg. per 100 cc.; on May 26, the nasal fluid (2 cc.) was turbid and colorless with a glucose content of 69 mg. per 100 cc. and a slight amount of epithelial debris. Roentgenograms of the skull (July 16) made in several positions after the injection of oxygen into the lumbar subarachnoid space, revealed enlargement of the sella turcica with possible slight communications with the paranasal sinuses in that region. The basal cisterns were well outlined, but none of the oxygen entered the lateral ventricles. There was a moderate amount of gas between the cerebral convolutions. Roentgenograms made 10 min. after the oxygen injection showed almost complete disappearance of the gas. A note on the chart stated: "This patient has a cerebrospinal-fluid leak into the nose, but whether or not the gas passed into the nose cannot be said." Spinal-fluid studies made after this procedure (July 16, 1948) showed a count per cubic millimeter of 7 cells, all lymphocytes (Fig. 4), with a total-protein concentration of 50 mg. per 100 cc.; the initial pressure was 370 mm. Hg; the final pressure was 100 mm. Hg. Operation was performed on July 16 for repair of a possible destructive bone lesion in the region of the sella turcica near the orbit and paranasal-sinus communications. The patient was discharged on July 25 with an initial lumbar-fluid pressure of 200 mm. Hg and a final pressure of 100 mm. Hg.

CASE 3.—R. M., a white man aged 36, was admitted to the hospital on June 26, 1948, with a history of continuous left-frontal headache since early May, 1948. His wife had noticed his grasping for words and their improper use for one month prior to his admission. The patient was right-handed and showed definite hand clumsiness, particularly noticeable in attempts to write. Glasses changed early in May for visual difficulties were no longer suitable. Neurologic examination showed hyperactive deep reflexes, a Babinski sign on the right and a suggestive right-facial lesion of supranuclear type. The optic disks were severely choked. Further questioning showed marked facetiousness and rambling speech, with definite grasping for words, clumsiness and drift of the right upper extremity. The impression was that of a tumor of the left frontal lobe, and, because of the short duration of symptoms, a glioblastoma multiforme was suspected. Spinal-fluid studies, a red-blood-cell count, white-blood-cell and differential counts, hemoglobin estimates, and serologic examinations all gave normal results. A ventriculogram done on July 6, after the injection of oxygen into the lateral ventricles, demonstrated a definite shift of the ventricular system away from the left side. The findings were suggestive of a large space-occupying mass, fairly far back and down in the left temporoparietal region. The third ventricle was slightly displaced but was otherwise not remarkable. Fluid aspirated from the left ventricle at this time was cloudy and blood-tinged and contained 1,150 red blood cells and 6 lymphocytes per cubic millimeter and 30 mg. of total protein per 100 cc. An occasional monocyte and lymphocyte were observed after fixation and staining by the Papanicolaou technique—Class-I smear (Fig. 5). The cytologic report was as follows: "There were no tumor cells in the left lateral ventricle and therefore probably no evidence of any tumor tissue projecting into the area of the left lateral ventricle. However, in view of the positive ventriculographic findings, this does not mean that there is no tumor present in the left temporoparietal region." Subsequently, a flap was turned and the left temporoparietal region explored. A large, ill-defined vascular mass was found, which microscopically showed many hyperchromatic nuclei with an occasional mitotic figure, multinucleated cells, pleomorphism, hemorrhagic extravasation and many atypical blood vessels throughout—all diagnostic of glioblastoma multiforme (Fig. 6).

7. Kolmer, J. A.: Clinical Diagnosis by Laboratory Examination, New York, D. Appleton-Century Company, Inc., 1943, pp. 329 and 333.

about 30 min. and gradually subsided without medication. At first, they involved the region of the nasal bridge but later became worse and of longer duration and involved the head bilaterally. She soon thereafter noticed loss of sense of smell and had difficulty in walking. Her gait became staggering; the right arm became paralyzed, and vision was gradually lost. She also stated that she had had several convulsive seizures. Just prior to admission she became lethargic, was unable to walk or see, and had had periods of dizziness when sitting upright or on moving the head. There had been some incontinence two days before her admission. Except for her exposure to poliomyelitis one year previously, the history was noncontributory. Physical examination showed the patient to be very thin, lethargic and semiconscious. The pupils were dilated and in equal diameter but did not respond to light; funduscopic examination revealed bilateral retinal hemorrhages, papilledema and engorgement of the retinal veins. The patient involuntarily moved the left arm and leg and the right leg; however, there was flaccid paralysis of the right arm. The rest of the examination was essentially noncontributory. Laboratory examinations, including a complete blood cell count, urinalysis, serological tests of the blood and the spinal fluid, and a 48-hr. culture of the spinal fluid, all gave normal results. A ventriculogram, made after the injection of oxygen into the lateral ventricles, showed moderate dilatation of these areas, without shift or displacement. However, there was rather pronounced dilatation of the third ventricle and the aqueduct of Sylvius. Oxygen was seen to pass into the subarachnoid portion of the spinal canal, indicating that, although there was no complete block to the flow of cerebrospinal fluid, a block of fairly high degree was obviously associated with the degree of dilatation observed. In addition, there was no shift of the third ventricle or the aqueduct. The changes were therefore believed to indicate the presence of a space-occupying mass low in the posterior fossa, associated with interference with cerebrospinal-fluid drainage. At operation, the right cerebellar hemisphere appeared to be pushed across the midline and the cerebellar tonsil herniated through the foramen magnum. On needle exploration, the entire right hemisphere appeared mushy. Bloody fluid was aspirated from the cisterna magna, smeared, and stained according to the Papanicolaou technique. The smears were graded as Class V and contained numerous large vesicular nuclei, some highly hyperchromatic with numerous mitoses and some arranged in what appeared to be pseudorosettes (Fig. 10). Further inspection of the lateral aspect of the right cerebellar hemisphere showed a reddish-gray tumor. Approximately the lateral third of this hemisphere, including the tumor, was removed. The patient's postoperative course was uneventful, and she was discharged on April 15. Microscopically, the tissue sections showed areas containing a lymphoid-like stroma, separated from each other by irregular Y-shaped connective tissue strands and occasional small blood vessels. The nuclei were pyknotic in some areas and vesicular in others. In some foci the tissue had the appearance of germinal centers of lymphoid follicles. Occasional groups of cells resembled pseudorosettes and lymphoid-type cells (Fig. 11). In one portion there was a thick capsule of fibrous tissue. My impression of the microscopic tissue was that of a medulloblastoma of the cerebellum; however, Dr. Harry M. Zimmerman, pathologist at Montefiore Hospital for Chronic Diseases, New York, said that one should also consider the possibility of a primary cerebellar sarcoma, of the intramural, perithelial or meningeal type. He suggested the use of Wilder's reticulum stain; this gave negative results.

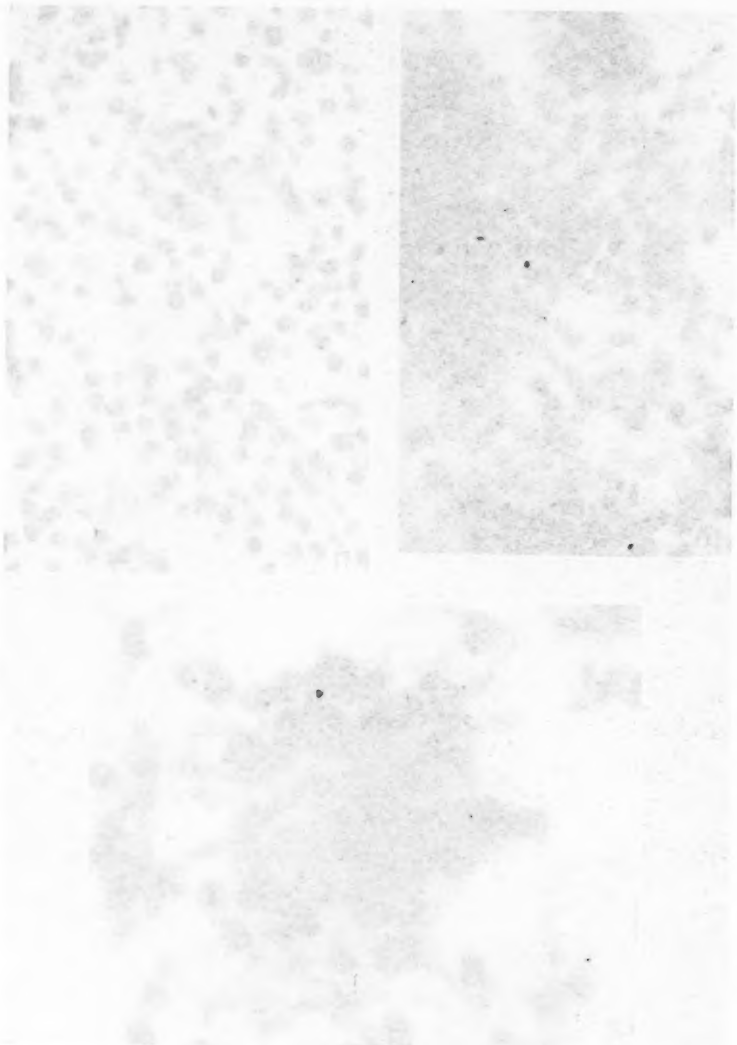
Case 7.—Mr. E. J. H., a white man aged 37, was admitted on Feb. 4, 1948, with the chief complaint of inability to move his legs. He was in good health until November, 1947, when he suddenly began to have severe occipital headaches. His legs subsequently became weak, with loss of control of them soon thereafter. X-ray therapy was given to the spinal areas (amount and location unknown). Thereafter spastic contraction of his lower extremities occurred, with associated intermittent urinary incontinence and gradual loss of bowel function. Physical examination showed the patient to be in some distress, with legs and thighs flexed in a spastic manner and feet plantar-extended. The temperature was 99.2 F.; the pulse rate, 112 per minute; the respiratory rate, 28 per minute; the blood pressure, 148/98. Neurologic examination revealed a bilateral Babinski sign, spastic contraction of both lower extremities, hyperactive patellar reflexes, paresthesia of the lower extremities, loss of vibratory and localized tactile sensation in both lower extremities, absence of superficial abdominal reflexes, and physiologically active deep reflexes in the upper portion of the lower extremities. The eyes reacted temporarily to light and in accommodation; there was no photophobia. Funduscopic examination showed increased reddening, some vascular nicking, and elevation of the central portion of the disks. No



Figs. 10-12.—*10* (Case 6), aspirated fluid from the cisterna magna, showing numerous vesicular nuclei, some extremely hyperchromatic nuclei with atypical mitoses and suggestive pseudorosette formation. The presence of these cytologic phenomena in this location suggested a possible cerebellar tumor desquamating into the cisternal space. × 470; Papanicolaou stain.

11 (Case 6), microscopic section from a reddish-gray tumor mass located in the lateral aspect of the right cerebellar hemisphere, revealing many lymphoid-type cells with pyknotic nuclei separated in many areas by fibroblasts. An occasional pseudorosette is also seen. Diagnoses of cerebellar medulloblastoma and primary cerebellar sarcoma were made. The Wilder stain for reticulum gave negative results. × 470; hematoxylin-eosin stain.

12 (Case 7), aspirated spinal fluid, showing fibrin and enmeshed hyperchromatic large nuclei, varying in size and shape, which evidently had been desquamated into the spinal subarachnoid space by a malignant neoplasm protruding therein or from above. × 970; Papanicolaou stain.



In an unselected series one observed an abnormal response. A specimen of a rapidly growing adenolymphoma sarcomatosus was made and examined by Dr. H. M. Thomson. The patient was discharged in an improved state on June 15, 1908.

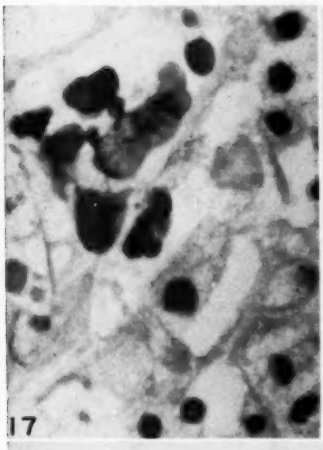
Case 9.—K. S., a 7-year-old girl was admitted to the hospital on June 6, 1902, with the following symptoms: Difficulty in both eyes and diplopia, in front of several years' duration. A history of mumps two months previously. On admission the left eyeball was normal in the position of rest, but on attempting to look to the left it moved only a little beyond the middle line, and on looking to the right, starting from the left, it moved with a distinct jerking movement at the end of the range. The jerks began by slow movement, followed by a rapid one, and continued persistently while fixation was retained in the abducted position. On attempting to look to the right with the left eye, the eyeball remained motionless. Similar movements were elicited in both eyes when looking upwards and downwards, but the amplitude of movement was greater. The right eyeball was normal in all directions. There was slight ptosis of the left upper lid. Pupils equal, responding normally to light and accommodation. Ophthalmoscopic examination showed no change in the fundus oculi. Vision was normal. Hearing was good in both ears. The tympanic membranes were normal. Tuning-fork tests showed that the left upper extremity was slightly weaker than the right. Both lower extremities were somewhat weak, and knee-jerks absent. Sensation was normal. A definite reaction of degeneration was obtained in the left deltoid. The lid and bulb were normally mobile. Tendon reflexes were present and equally active on both sides. The knee-jerks were absent. Plantar reflexes were normal. Pupillary reactions were normal. The urine showed no abnormality. The patient was discharged on June 15, 1902, with the eyeball movements unchanged.

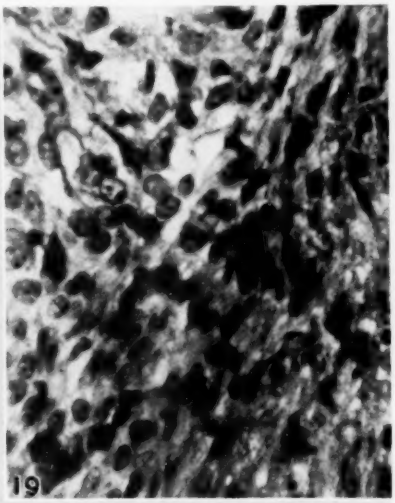
Case 10.—E. S., a 7-year-old girl, was admitted to the hospital on March 12, 1918, complaining of transient paralysis of shoulder and weakness of the left side of the body. He

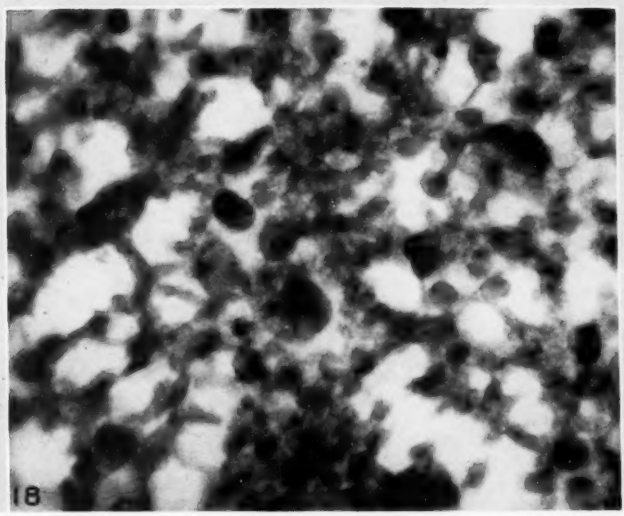
In an occasional zone one observed atypical capillary channels. A diagnosis of a rapidly growing glioblastoma multiforme was made and confirmed by Dr. H. M. Zimmerman. The patient was discharged in an improved state on June 6, 1948.

Case 9.—R. S., a 7-yr.-old white girl was admitted to the hospital on Feb. 4, 1948, with the chief complaint of progressive increase in head size and difficulty in gait of several years' duration. A history of normal birth was obtained; however, the child was much slower than normal in her learning to walk, which occurred at 13 mo. of age. She seemed to stagger toward the right, carrying her head on her right shoulder, and was ataxic. These symptoms occurred in definite attacks, lasting from a few days to two weeks, with a clear-cut remission at the end of the relapse. One year before her admission, a considerable increase in the head size and frequent generalized mild intermittent headaches, not related to head positioning, were noted. Simultaneously the child had diminution of visual acuity. A few weeks before her admission there had been noticed increased urination without excessive thirst or fluid intake. Physical examination showed the patient to be cooperative, well-developed and well-nourished, appearing younger and smaller than a child of the stated age. The head showed considerable fulness, especially in the temporal squama. A definite crackpot sound (Macewen's sign) was elicited on percussion of the skull. The fat and hair were normally distributed. Funduscopic examination showed early bilateral papilledema. There was also a supranuclear type of left-facial paralysis, most noticeable on motion expression. The tongue protruded to the left of the midline. Examination of the motor system showed that the left upper extremity was definitely weaker than the right. Both lower extremities were somewhat weak, and their reflexes showed considerable hyperactivity, with unsustained patellar and ankle clonus bilaterally. The Babinski sign was present bilaterally. There was also slight hyperactivity of the deep reflexes in the left upper extremity. The Hoffmann sign was not present. The arms showed no tendency to drift on extension. Coordination tests showed a definite tendency to fall to the right and ataxia of gait, as well as pronounced ataxia in the heel-to-knee test bilaterally. The finger-to-nose test was done fairly well, and there were no signs of adiadokokinesia or dysmetria. Sensory examination showed a normal status. All laboratory examinations were noncontributory except for the demonstration in the stools of numerous fertilized ova of Ascaris lumbricoides and small round worms, measuring approximately 0.4 by 8.5 cm. Roentgenologic examination of the skull showed many calcium flecks deep in the right posterior-parietal pineal region. Most of them were to the right of the midline. The sella turcica was greatly enlarged, and the convolutional markings were prominent, indicating a high degree of increased intracranial pressure. When the films were reviewed with Dr. Percival Bailey, the possible diagnoses of a teratoid tumor of the pineal gland (because of calcification), craniopharyngioma and histoplasmosis were considered. On Feb. 11, a bone flap was turned down in the right parietal region and the dura incised. On needling the brain, a large cyst was entered at an approximate depth of 0.5 cm. It contained approximately 120 cc. of yellowish fluid, high in protein content. Decompression was accomplished by evacuation of the cyst. Smears from this fluid, fixed and stained according to the Papanicolaou technique, showed numerous large nuclear structures, some fused, some undergoing mitosis, and some hyperchromatic and vesicular (Fig. 18). These cells were thought to have been desquamated from the wall of the cyst and were considered diagnostic of a cerebral malignant growth (Class IV-V). A linear incision made through the cortex posterior to the postcentral gyrus, directly over the tumor mass, revealed a large cystic cavity filled with gelatinous material, especially anteriorly. A small daughter cyst was also present at the inferior portion of the major cyst; it contained approximately 30 cc. of fluid. Because of the poor operative state of the patient and the extensive involvement, no attempt was made to remove the tumor completely. Microscopic study of biopsy specimens showed marked palisading and parallel arrangement of fibroblast-like cells with vesicular and hyperchromatic nuclei. Little vascularity was present. Occasional mitoses were seen (Fig. 19). These sections were reviewed by the Army Institute of Pathology (Dr. Webb Haymaker), who believed them to be representative of a rapidly growing astrocytoma, probably of the astroblastoma type; Dr. H. M. Zimmerman, who also reviewed them, believed them to be from an astrocytoma superimposed on a congenital malformation.

Case 10.—P. S., a white man aged 42, was admitted to the hospital on March 17, 1948, complaining of recurrent episodes of headache and weakness of the left side of the body. He



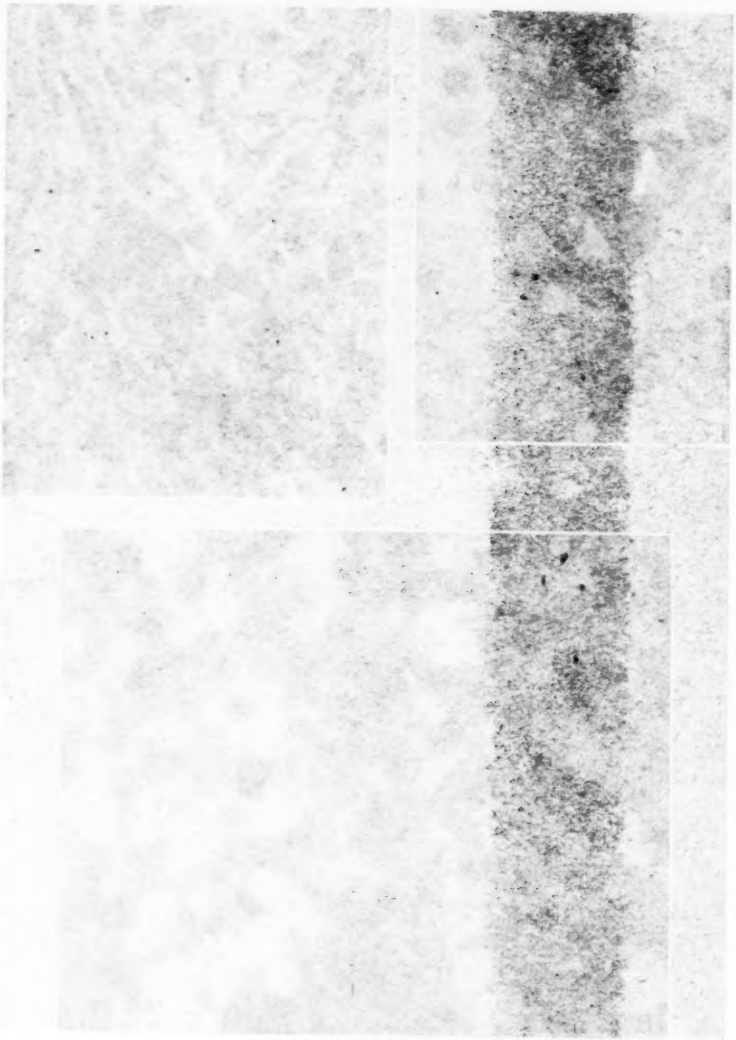




Figs. 17-19.—*17* (Case 8), biopsy specimen through cerebral cyst wall and adjacent tissue, showing large ganglion-type cells with associated marked pleomorphism, suggestive of a rapidly growing glioblastoma multiforme. × 470; hematoxylin-eosin stain.

18 (Case 9), aspirate from cerebral cyst from the cortex of the right postcentral gyrus, showing numerous large hyperchromatic and vesicular nuclear structures, some fused, some with prominent nucleoli, and an occasional one undergoing mitosis. These cells were thought to have been desquamated from the cyst wall of the tumor and were considered to be of a Class-IV variety. × 470; Papanicolaou stain.

19 (Case 9), palisading of fibroblast-like cells with vesicular and hyperchromatic nuclei and very little vascularity, a pattern compatible with the diagnosis of astrocytoma. Biopsy specimen from wall of cerebral cyst posterior to right postcentral gyrus; × 470; hematoxylin-eosin stain.

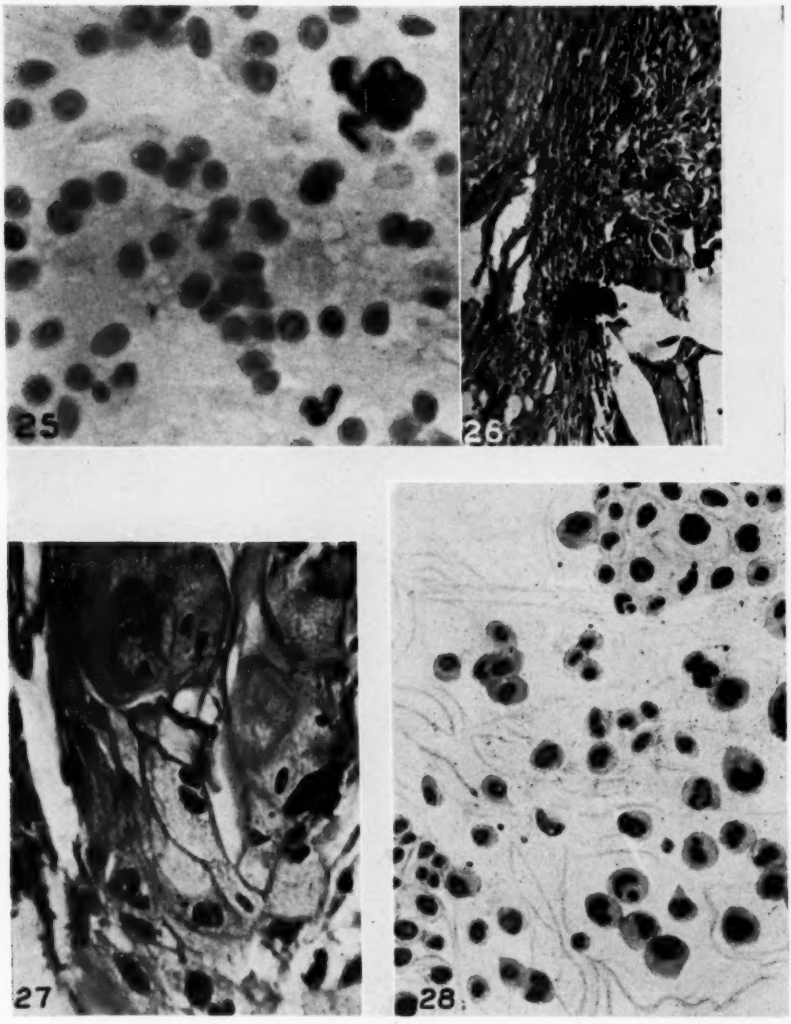


ventricles and pneumoencephalograms showed very decided shift of the third and lateral ventricles away from the left side, with an associated slight degree of dilatation, indicative of a tumor fairly low down in the left temporal region (Wernicke's area). A bone flap was made. The dura appeared to be tense over the above-described area, and on further examination a tumor was observed just anterior to the left Sylvian fissure in the second-face area. Exploration with a brain needle revealed that the tumor mass extended a large cyst, from which approximately 20 cc. of rapidly clotting, thick, yellowish fluid was removed. Smears of this fluid, utilizing the Papanicolaou technique and slide, showed several sheets of malignant cells with large nuclei and prominent nucleoli (Figs. 22 and 23); the diagnosis was Class IV-V malignancy. Aspiration of the contents of the left lateral ventricle revealed similar groups of malignant cells. Gross examination of the tumor itself at this time showed involvement of almost the entire frontal lobe with apparent extension into the frontal horn of the lateral ventricle on the left side. Microscopic study of tissue removed showed moderate pleomorphism, variation in nuclear size and shape, many mitoses, and spindle-shaped cells, with associated palisading around new, irregularly shaped small vessels (Fig. 24). A diagnosis of a rapidly growing glioblastoma multiforme was made. Postoperative irradiation was advised.

CASE 6.—R. M., a 5-year-old white boy, was admitted with a history of headache starting approximately five and one-half to six months before admission to the hospital. Unsteadiness in gait, blurred vision, and diplopia were observed seven to 10 mo. before admission. Physical examination revealed an internal rotation of the right eye. Because of the child's apprehensive state, adequate eye examination was not possible, and therefore the visual fields were not accurately determined. The temperature was 98 F., the pulse rate, 92 per minute, and the respiration rate, 24 per minute. The patient weighed 37 pounds (16.8 kg.) and was 42½ inches (108 cm.) in height. The hemogram, urologic findings and feces were all normal. The glucose level of the blood was 96 mg. per 100 cc. The chloride measured 550 mg.; the total cholesterol, 167 mg.; the calcium, 12 mg., and the phosphorus, 4.08 mg., per 100 cc. The glucose-tolerance test revealed a level of 140 mg. per 100 cc. at the end of two hours and of 50 mg. at the end of three and one-half hours. The spinal fluid was clear, colorless, and free of cells; the reaction for globulin was negative, the colloidal gold curve was normal, and the total-protein content was 25 mg. per 100 cc. A roentgenogram of the skull showed a definite abnormality in the region of the dorsum sellae and the posterior clinoid processes. There was also an area of amorphous calcification apparently lying within the sella. All these findings were thought to indicate intrasellar erosion, apparently from a pituitary tumor of some type in which there were calcium deposits. At the time of operation an incision was made in the dura of the right frontal area. Very thin ivory-colored fluid was aspirated from the ventricular cavity of the tumor. This procedure was instituted in order to accomplish decompression of an obvious hydrocephalus. After the fluid was drained a cyst was observed. Fluid aspirated from this structure was slightly turbid and contained obvious cholesterol crystals. Further examination of the fluid stained by the Papanicolaou technique demonstrated numerous large single and multinucleated, foam-appearing cells with hyperchromatic and pyknotic nuclei (Fig. 25). The smear was graded Class III-IV. On dissection, a solid part of the tumor was withdrawn from its position on the roof of the sella and between the optic chiasm. The cystic portion was then seen lying just superior to this mass and was likewise teased out. It was found to be adherent to the right optic nerve, and some dissection was necessary to obliterate it. Grossly the specimen consisted of a cystic, yellowish-brown mass, measuring 2 by 1 cm. in diameter, with several gritty small particles over the surface. Microscopically the section was composed of pieces of tissue lined by an irregular type of stratified squamous epithelium. Deeper portions of the epithelium had a pearl-like arrangement, with eosinophilic-staining cells containing distinct intercellular bridges. Keratohyalin-like granules and calcific cholesterol deposits were also seen in many areas (Figs. 26 and 27). A diagnosis of cyst of Rathke's pouch with degenerative changes was made and was confirmed by Dr. Harry M. Zimmerman. The patient's postoperative course was progressively downhill, and seven weeks later he died. Autopsy revealed a subdural hematoma in the right temporoparietal region, moderate encephalomalacia of the right frontal lobe, thrombosis of the right cavernous sinus, and bilateral pulmonary congestion.

ventricles, and ventriculograms showed very decided shift of the third and lateral ventricles away from the left side with an associated slight degree of dilatation, indicative of a tumor fairly low down in the left temporal region (Broca's area). A bone flap was made. The dura appeared to be tense over the above-described area, and on further examination a tumor was observed just superior to the left Sylvian fissure in the frontal-lobe area. Exploration with a brain needle inserted into the tumor mass revealed a large cyst, from which approximately 20 cc. of rapidly clotting, thick, yellowish fluid was removed. Smears of this fluid, utilizing the Papanicolaou technique and stain, showed several sheets of malignant cells with large nuclei and prominent nucleoli (Figs. 22 and 23); the diagnosis was Class IV-V malignancy. Aspiration of the contents of the left lateral ventricle revealed similar groups of malignant cells. Gross examination of the mass itself *in situ* showed involvement of almost the entire frontal lobe with apparent projection into the frontal horn of the lateral ventricle on the left side. Microscopic study of tissue removed showed moderate pleomorphism, variation in nuclear size and shape, many mitoses, and spindle-shaped cells, with associated palisading around new, irregularly shaped blood vessels (Fig. 24). A diagnosis of a rapidly growing glioblastoma multiforme was made. Postoperative irradiation was advised.

Case 12.—S. S., a 2-yr.-old white boy, was admitted with a history of headache starting approximately five and one-half to six months before admission to the hospital. Unsteadiness in gait, failing vision, and diplopia were observed seven to 10 mo. before admission. Physical examination revealed an internal squint of the right eye. Because of the child's apprehensive state, funduscopic examination was not possible, and therefore the visual fields were not accurately determined. The temperature was 97 F.; the pulse rate, 82 per minute, and the respiration rate, 20 per minute. The patient weighed 27 pounds (12.2 kg.) and was 34½ inches (86 cm.) in height. The hemogram, serologic reactions and urine were all normal. The glucose level of the blood was 96 mg. per 100 cc. The chlorides measured 530 mg.; the total cholesterol, 167 mg.; the calcium, 12 mg., and the phosphorus, 0.88 mg., per 100 cc. The glucose-tolerance test revealed a level of 100 mg. per 100 cc. at the end of two hours and of 56 mg. at the end of three and one-half hours. The spinal fluid was clear, colorless, and free of cells; the reaction for globulin was negative; the colloidal gold curve was normal, and the total-protein content was 25 mg. per 100 cc. A roentgenogram of the skull showed a definite abnormality in the region of the dorsum sellae and the posterior clinoid processes. There was also an area of amorphous calcification apparently lying within the sella. All these findings were thought to indicate intracellular erosion, apparently from a pituitary tumor of some type in which there were calcium deposits. At the time of operation an incision was made in the dura of the right frontal region over the second convolution, and fluid was aspirated from the ventricular cavity of this area. This evacuation was completed in order to accomplish decompression of an obvious hydrocephalus. Anterior to the optic chiasm a cyst was observed. Fluid aspirated from this structure was slightly turbid and contained obvious cholesterol crystals. Further examination of the fluid stained by the Papanicolaou technique demonstrated numerous large single and multinucleated, fused epithelial cells with hyperchromatic and pyknotic nuclei (Fig. 25). The smear was graded Class IV-V. On dissection, a solid part of the tumor was withdrawn from its position on the roof of the sella and between the optic chiasm. The cystic portion was then seen lying just superior to this region and was likewise teased out. It was found to be adherent to the right optic nerve, and sharp dissection was necessary to obliterate it. Grossly, the specimen consisted of a cystic, pinkish-brown mass, measuring 2 by 1 cm. in diameter, with several gritty ovoid particles over the surface. Microscopically the section was composed of pieces of tissue lined by an irregular type of stratified-squamous epithelium. Deeper portions of the epithelium had a pearl-like arrangement, with eosinophilic-staining cells containing distinct intercellular bridges. Keratohyalin-like granules and calcific-cholesterol deposits were also seen in many areas (Figs. 26 and 27). A diagnosis of cyst of Rathke's pouch with degenerative changes was made and was confirmed by Dr. Harry M. Zimmerman. The patient's postoperative course was progressively downhill, and seven weeks later he died. Autopsy revealed a subdural hematoma in the right temporoparietal region, moderate encephalomalacia of the right frontal lobe, thrombosis of the right cavernous sinus, and bilateral pulmonary congestion.

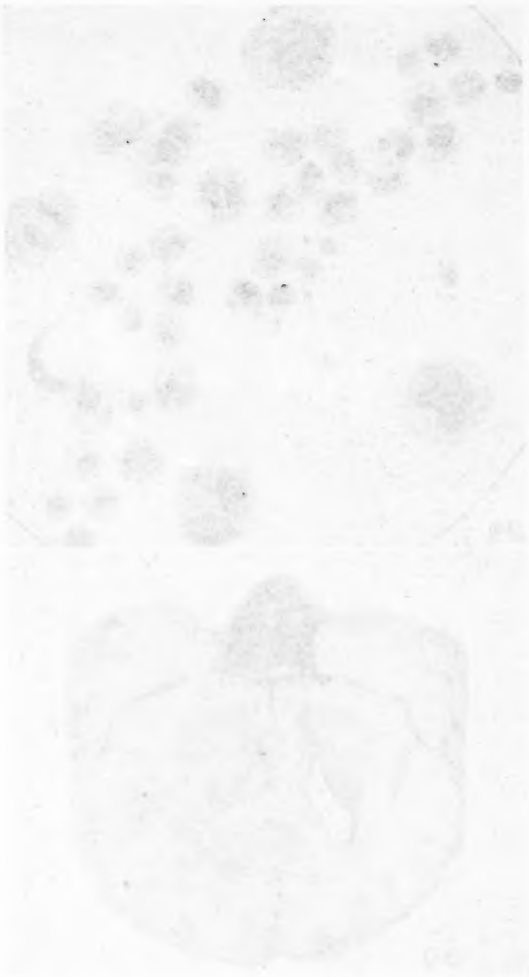


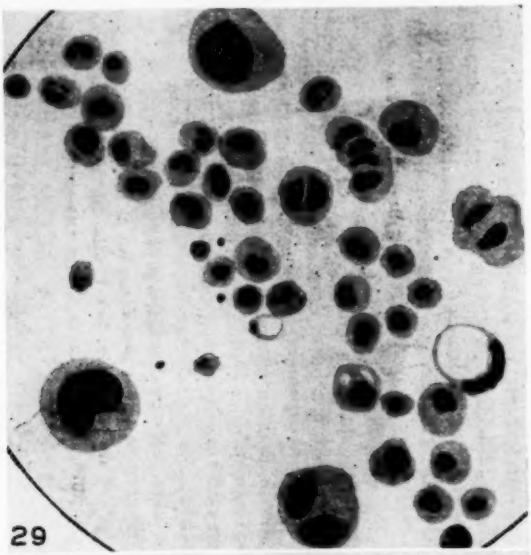
Figs. 25-28.—*25* (Case 12), cystic fluid from pituitary region, showing a large multinucleated cell, possibly due to fusion of several atypical epithelium-like cells. Erythrocytes and other types of epithelial and inflammatory cells are also observed. × 470; Papanicolaou stain.

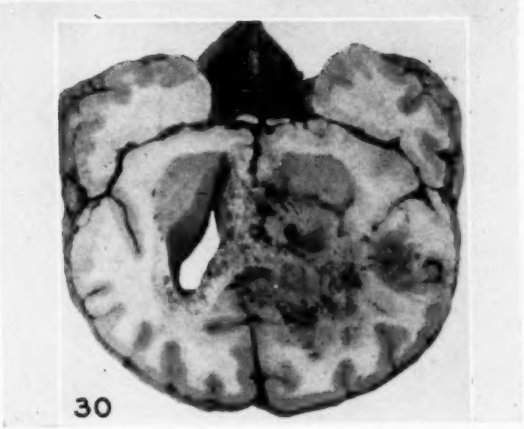
26 (Case 12), biopsy tissue from wall of the cyst, showing partial erosion of epithelial surface lining, with pearl-like formation, by eosinophilic staining cells possessing distinct intercellular bridges. A diagnosis of cyst of Rathke's pouch with degenerative and inflammatory changes was made. × 100; hematoxylin-eosin stain.

27 (Case 12), higher magnification of portion of field in *26*, showing keratohyalin-like granules and calcific-cholesterol deposits. × 470; hematoxylin-eosin stain.

28, plate showing tumor epithelial cells, arranged singly and in clumps, sketched by Humbert and Alexieff [28] (Fig. 3, p. 954). Smears were from the cerebrospinal fluid of a living patient who had a primary carcinoma of the breast with cerebral metastases and diffuse meningeal carcinomatosis.

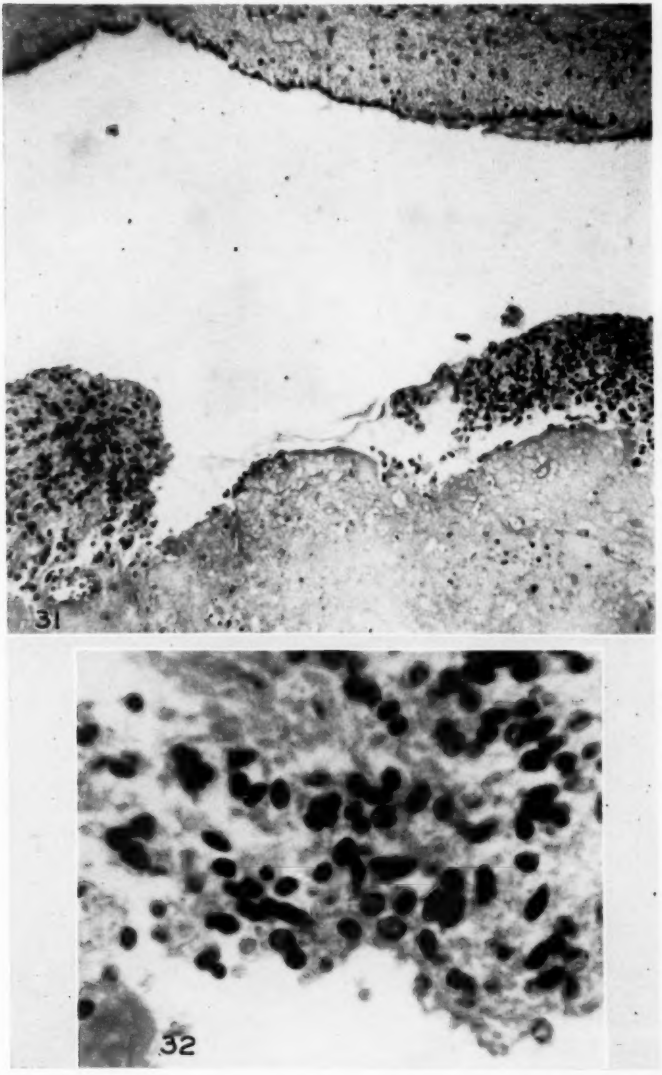






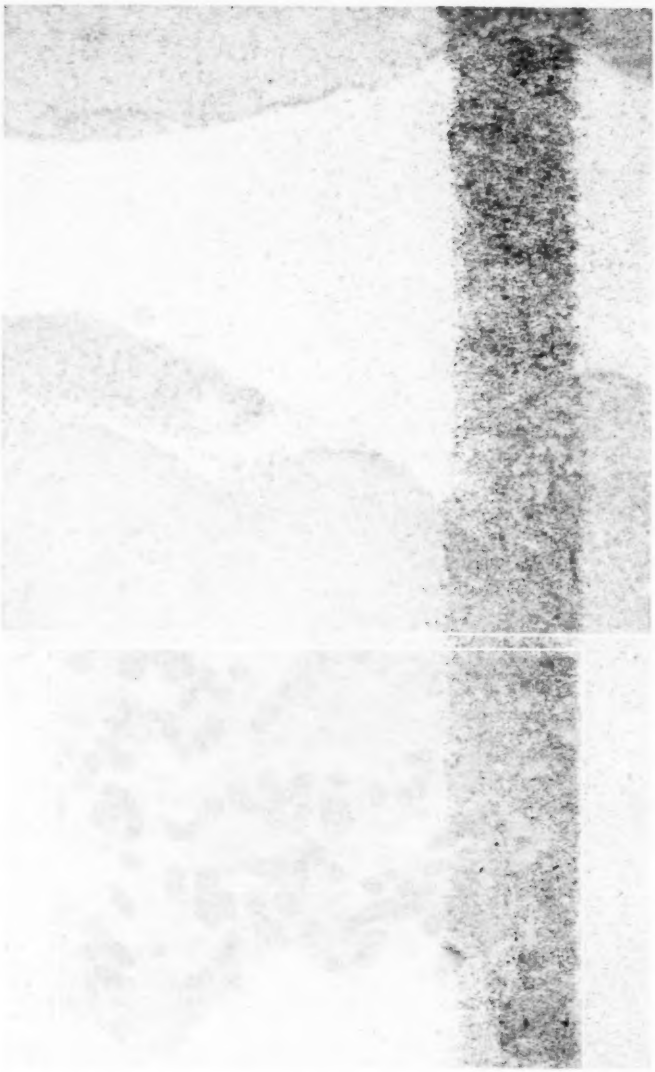
Figs. 29-30.—*29*, another field from the case of Humbert and Alexieff [28] (Fig. 1, p. 950). Note comparative size and structure of cells of granulocytic series.

30, gross specimen, showing how and why tumor cells may be found in fluid aspirated from the lateral and other ventricles. In this figure, one observes a destructive glioblastoma multiforme with large blood vessels, yellow regions of necrosis and cystic spaces filled with thick greenish fluid, extending from one part of the brain through one lateral ventricle across the septum pellucidum and pushing up into, and possibly through, the ependymal lining of the opposite lateral ventricle. Reproduced from Figure 202: Blackwood, W.; Dodds, T. C., and Sommerville, J. C.: Atlas of Neuropathology, Edinburgh, E. & S. Livingstone, Ltd., 1949, by permission of the publisher.



Figs. 31-32.—*31*, microscopic demonstration of a glioblastoma multiforme extending into the lumen of the third ventricle with desquamation of malignant tumor cells therein. NA 46-49; × 100; hematoxylin-eosin stain.

32, higher magnification of portion of field in *31*, showing actual infiltration and desquamation of neoplastic cells into the lumen of the third ventricle. × 470; hematoxylin-eosin stain.



which the tumor arose in the fourth ventricle. According to these authors, in each of the six cases in which implantation occurred a "tongue" of tumor tissue projected from the fourth ventricle through the cisterna magna into the spinal subarachnoid space at the level of the foramen magnum, and in some instances as far as the second cervical segment. This observation again lends support to the theory that desquamation occurs as a result of bathing of the tumor tissue by the spinal fluid. Perhaps it would also be logical to conclude that movement of the head, coughing, sneezing, and minor trauma of the head could dislodge tumor cells into the spinal fluid. Some neurosurgeons also believe that surgical intervention and aspiration might be implicated in producing exfoliation,[30] with possible tumor seeding along the aspiration track. In most instances seeding of the ventricles and subarachnoid spaces occurs more frequently with the rapidly growing gliomas; symptoms may or may not be produced by these implants.[31] Finally, the possibility that disseminated carcinomatosis of the spinal meninges can occur without any demonstrable cerebral neoplasm was reported by Hoffmann, as cited by Willis.[6] Knierim,[32] and Alpers and Smith [33] have attributed the meningeal infiltration to invasion of the meninges from without by way of nerve sheath, nerve roots, and possibly perineural lymphatics. However, it is also possible that minute, undiscovered blood-borne metastases in the brain, choroid plexus, or meninges may have been the route of the meningeal spread, with subsequent exfoliation of cells into the subarachnoid space and spinal fluid.

Another locus for the study of exfoliated cells in the central nervous system is the cerebral cyst. Although several varieties of such cysts may be encountered at operation—congenital, inflammatory (occasionally a specific diagnosis may be made by needle exploration of the inflammatory cyst just before the calvaria flap is turned, Spurling,[34] for example, citing a case in which a pure culture of Eberthella typhi was isolated from pus aspirated from such a cerebral cyst), traumatic, parasitic (Fig. 34), degenerative, and neoplastic—the most important and commonest group is the neoplastic. According to Craig and Kernohan,[35] the gliomatous cyst usually contains xanthochromic fluid and frequently presents a small or a large intramural tumor (Fig. 35). The other cysts, except for those associated with arteriosclerosis and subsequent liquefaction of the infarct, more frequently contained a clear fluid. Of course, the final differential diagnosis of the nonneoplastic type of cyst must be made by serious consideration of the antecedent history. The same authors [35] also discussed other important points associated with the cytology and etiology of

30. Svien and others.[27] Groff, R. A., in discussion on Platt, W. R.: Exfoliative Cytological Diagnosis of Lesions in the Central Nervous System, Arch. Neurol. & Psychiat. **65**:249-250 (Feb.) 1951.

31. Tarlov and Davidoff.[25] Svien, Gates and Kernohan.[27]

32. Knierim, G.: Über diffuse Meningealkarzinose mit Amaurose und Taubheit bei Magenkrebs, Beitr. path. Anat. **44**:409-429, 1908.

33. Alpers, B. J., and Smith, O. N.: Carcinomatosis of the Meninges of the Spinal Cord and Base of the Brain Without Involvement of the Parenchyma, Secondary to Carcinoma of the Lung, Am. J. Cancer **32**:361-366, 1938.

34. Spurling, R. G., cited by Love, J. G., and Kernohan, J. W.: Dermoid and Epidermoid Tumors (Cholesteatomas) of Central Nervous System, J. A. M. A. **107**:1876-1883 (Dec. 5) 1936.

35. Craig, W. M., and Kernohan, J. W.: Cerebral Cysts, J. A. M. A. **102**:5-11 (Jan. 6) 1934.

Fluid Aspirated	Tumor-Negative Cytology	Tumor-Positive Cytology
Ventricular	Normal cytology: Occasional monocyte, lymphocyte, endothelial cell, erythrocyte, and/or polymorphonuclear leukocyte, indicating no tumor exfoliating into the ventricular cavities, if: (*a*) Brain abscess: excess number of polymorphonuclears and/or lymphocytes (*b*) Lymphocytic choriomeningitis: Excess number of lymphocytes (*c*) Encephalitis (syphilitic, tuberculous, virus or rickettsial infections): Usually a large number of monocytes and/or lymphocytes with an occasional polymorphonuclear cell (*d*) Extending intracerebral hemorrhage: Usually a large number of normal, crenated, and hemolyzing erythrocytes throughout smear, with an occasional polymorphonuclear cell or lymphocyte	Large nuclear structures (10-20 μ) with prominent nucleoli and chromatin network; nucleus-cytoplasm ratio approximately 3:1 (marked increase); cells occasionally seen as clumps and sheets. Changes, when present, indicative of a tumor process, desquamating into ventricular cavities, e. g., glioblastoma multiforme, ependymoma, medulloblastoma, astrocytoma, oligodendroglioma, retinoblastoma, pinealoma, or metastatic carcinoma
Cisterna magna	Normal cytology: Same as above, indicating no tumor present or no tumor cells desquamating into cisternal space, if: (*a*) Subarachnoid hemorrhage, vascular tumor (Lindau, etc.), or extending intracerebral hemorrhage: Usually large numbers of normal, crenated, and hemolyzing erythrocytes throughout smear with occasional polymorphonuclear or lymphocyte (*b*) Leptomeningitis, meningoencephalitis or extending brain abscess: Usually excess numbers of polymorphonuclears and occasional lymphocytes and monocytes; Gram and acid-fast stains may reveal specific bacteria, e. g., meningococci, H. influenzae, streptococci, staphylococci, pneumococci, Pseudomonas aeruginosa, Friedländer's bacillus, fusiform bacilli, Mycobacterium tuberculosis, Proteus vulgaris, and E. coli. Serologic tests done to detect syphilitic infection. Occasionally protozoan etiology—e. g., Entameba histolytica and Toxoplasma. Occasionally fungus infections—e. g., Coccidioides immitis. Cryptococcus hominis, Actinomyces bovis, monilia albicans, etc. If all the above negative may have to resort to serological, rickettsial and virus infection studies.	Cytology same as above, indicating tumor cells exfoliating into ventricular cavities and subsequently into cisternal space, e. g., same tumors as those listed above. May also represent a primary neoplasm in that area, e. g., sarcomatosis of the meninges, meningioma, cerebellopontile angle tumor (neurofibroma, etc.), occasionally pituitary tumors (adenoma and carcinoma) and cerebellar medulloblastoma
Spinal canal	Normal cytology and/or cellular pattern, as above, indicates similar etiologic agents, as well as probable absence of any tumor process in spinal canal; however, there is the possibility that a tumor may be present which is not desquamating into the spinal subarachnoid space	Cytology same as that of ventricular and cisternal areas, indicating tumor-cell desquamation above level of spinal puncture from above-listed tumors. May also represent exfoliation from secondary seeding on spinal-cord membranes, e. g., medulloblastoma, astrocytoma, and ependymoma, as described above; also lymphoblastoma or metastatic carcinoma (prostate, 22%; breast, 19%; lung, 12%; uterus, 3.5%). May also represent primary cord tumor or vertebral tumor extending into subarachnoid space and desquamating therein. Cord tumors, in order of frequency: neurofibroma, neurinoma, meningioma and extramedullary neoplasms, such as ependymoma, oligodendroglioma, medulloblastoma, polar spongioblastoma, glioblastoma multiforme and neuroblastoma. Vertebral tumors: chordoma, osteogenic sarcoma, liposarcoma and metastatic-tumor processes
Cerebral and cerebellar cysts	Usually clear fluid aspirated, which may contain an occasional microglial cell, epithelial or mesothelial cell, monocyte, polymorphonuclear leukocyte, erythrocyte, spore, and/or parasite. Types of nonneoplastic cerebral cysts observed[85] 1. Congenital, e. g., porencephalic, epidermoid and simple 2. Inflammatory, e. g., end-result of cerebral-abscess formation (fluid may be turbid or purulent) 3. Traumatic, e. g., calcified cysts (following subcortical hematoma), simple cyst, and subdural hematoma (questionably included). Fluid may be xanthochromic or hemorrhagic 4. Parasitic, e. g., Echinococcus granulosus; Cysticercus cellulosae. (May also see an increase in eosinophils and mononuclear cells in aspirated fluid) 5. Arteriosclerotic (really liquefied infarcts)	Aspirated fluid from neoplastic cysts may be xanthochromic with occasional erythrocytes and leukocytes in all stages of degeneration. Exfoliated tumor cells, if present, may be individual or in clumps, as described above. Commonest, in order of occurrence, are ependymomas, spongioblastoma, astrocytoma, gangliocytoma and meningioma.[85] Occasional cerebellar cyst, usually astrocytoma in type

MALIGNANT TUMORS IN THE INSTITUTIONALIZED PSYCHOTIC POPULATION

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CONSIDERABLE research has been done on the relation of personality structure to such elements of constitution as body habitus, endocrine responsivity and autonomic reactivity. There have been many indications that it might also be fruitful to correlate trends of cellular pathology with personality reactions. Previous work tends to direct particular interest to malignant tumors.

Lewis [1] divided schizophrenic patients, on the basis of their mental reaction types, into two groups: (1) "regressive," comprising the catatonic and hebephrenic reaction types, and (2) "hypercompensatory," embracing the paranoid types. He then studied the extraneural pathology of each group and concluded that in the former group atrophy, hypoplasia and fibrosis, but rarely malignant changes, is characteristic, whereas the latter group tends toward hypertrophy, hyperplasia and malignant change. These groups are antithetical, but within each group the direction of the psychic and pathological trends is analogous. As cited by White,[2] he characterized this correlation with the phrase, "cancer is paranoia at the cellular level."

White,[2] dividing patients into paranoid, cyclic and schizoid reaction types, lent partial confirmation, reporting that there were 136 malignant tumors per 1,000 deaths in the paranoid group, as opposed to 112 in the cycloid and 43 in the schizoid group. Chevens [3] reported a relatively higher incidence of cancer in patients with nonschizophrenic paranoid conditions. More recently Sheldon [4] reported that the mesomorphic (the primarily muscular) body habitus tends to a relatively higher incidence of both paranoid reactions and malignant tumors. These observations of Lewis on paranoid reactions have stimulated considerable interest. All the conclusions cited on the incidence of malignant tumors, however, are based on proportionate mortality rates. For this reason, as will be shown, their reevaluation is warranted.

On the other hand, Lewis' finding that the regressive group has a low incidence of malignant tumors has apparently not been subjected to further study.

There has also been little work on the correlation of cancer incidence with the psychic reaction types as defined in the usual diagnostic categories of clinical

From the Research Service, Worcester State Hospital.

1. Lewis, N. D. C.: Research in Dementia Praecox (Past Attainments, Present Trends and Future Possibilities), New York, National Committee for Mental Hygiene, 1936.

2. White, W. A.: The Social Significance of Mental Disease, Arch. Neurol. & Psychiat. **22**:873 (Nov.) 1929.

3. Chevens, L. C. V.: J. Ment. Sc. **77**:562, 1931.

4. Sheldon, W. H.: Varieties of Delinquent Youth, New York, Harper & Brothers, 1950.

psychiatry. Neubürger [5] has done this for the psychoses associated with cerebral arteriosclerosis, concluding that carcinoma is a great rarity. Chevens [3] and Hahnemann [6] investigated schizophrenia, paranoid conditions, manic-depressive psychoses and mental deficiency, finding a low incidence in the mentally defective and the schizophrenic groups. These studies also are based on proportionate mortality figures. In contrast, Opsahl [7] reported a high incidence of cancer associated with schizophrenia.

Studies which deal with cancer in psychiatric hospital populations as a whole are numerous. Interest was undoubtedly heightened by a series of investigations which seemed to show that cancer was rare in such populations. The value of such studies is limited, as they aggregate such diversified entities as schizophrenia, mental deficiency and neurosyphilis. In accordance with the findings in the majority of these papers, there is apparently a prevalent impression that cancer is rare among psychiatric hospital patients. In 1941, however, Peller and Stephenson [8] reported that at St. Elizabeths Hospital cancer had become commoner than tuberculosis as a cause of death. There is need to reevaluate critically the opinion that cancer is rare in psychiatric hospital patients.

Previous investigations on the frequency of cancer in psychotic patients can be divided into two groups, which have antithetical results. One group reports that the incidence of cancer in psychiatric hospital patients is slightly higher than in the general population; the other, that it is decidedly lower. None of the investigators reports a result between these extremes. It can be shown that this discrepancy is a result of the use of different statistical methods. A low incidence will be consistently found by basing the result on proportionate mortality rates; a higher incidence, when cancer death rates are employed. There is great confusion about these methods. This matter is so basic and vital that I shall digress at this point to discuss it.

Proportionate mortality rates are computed as follows:

$$\text{Proportionate mortality rate} = \frac{\text{Number of deaths from cancer}}{\text{Number of deaths from all causes}} \times 100$$

The cancer death rate is usually computed thus:

$$\text{Cancer death rate per annum} = \frac{\text{Number still living at end of one year}}{\text{Number of deaths from cancer during that year}}$$

In Massachusetts the annual death rate is about seven times as great in the institutionalized psychotic population as it is in the general population. This higher death rate obtains elsewhere in the United States and in the British Isles.[9] Populations can be compared for specific causes of death on the basis of proportionate mortality rates only when they have equal or nearly equal death rates. In other

5. Neubürger, K.: Beiträge zur Histologie, Pathogenese und Einteilung der arteriosklerotischen Hirnerkrankung, Jena, Gustav Fischer, 1930.

6. Hahnemann, J.: Ugesk. læger **93**:1132, 1931.

7. Opsahl, R.: Norsk. mag. lægevidensk. **94**:771, 1933.

8. Peller, S., and Stephenson, C. S.: Pub. Health Rep. **56**:132 (Jan.) 1941.

9. (*a*) Mental Patients in State Hospitals, United States Department of Commerce, United States Bureau of Census, 1928-1942. (*b*) Mortality Statistics, United States Department of Commerce, Bureau of the Census, 1929-1942. (*c*) Pool, A.: J. Ment. Sc. **76**:234, 1930. (*d*) Lord, J. R., and McGrath, M. J.: J. Ment. Sc. **76**:223, 1930.

words, if the members of one population are dying seven times as fast of tuberculosis, for instance, as those of another, they will not survive to die of cancer. Proportionate mortality rates, based on the total deaths, are dependent, then, on the death rate from all other conditions. However, since the death of any member of a population "affects the number dead and the number living in the same proportion,"[10] cancer death rates are not affected by the total death rate (unless extreme), and populations with differing death rates are comparable. The use of cancer death rates in studies of this type thus becomes imperative.

The significant publications[11] on the incidence of cancer in psychiatric hospitals are summarized in table 1. All of them must be evaluated in terms of the statistical method used. A scrutiny of the table reveals a striking difference between the results in studies of group 1, which utilize proportionate mortality rates, and in studies of

TABLE 1.—*Summary of Literature on Incidence of Malignant Tumors in Psychiatric Hospital and Comparable General Populations*

Author	Incidence (%) of Malignant Tumors in Psychotic Population	Incidence (%) of Malignant Tumors in General Population
Group 1: Studies Based on Proportionate Mortality Rates and Autopsy Diagnoses		
Pool [11a]	3.7	12.0 *
Report of Board of Control [11k]	3.4	12.4
Hahnemann [6]	5.5	15.1
Büel [11d]	6.5	13.0 †
Warren and Canavan [11e]	4.3	13.1
Chevens [3]	7.0	....
Lucksch [11g]	2.7	3.7 ‡
Group 2: Studies Based on Cancer Death Rates (per 1,000) and Clinical Diagnoses of Cancer		
Copeman and Greenwood [11b]	1.58	1.34
Rudolph and Ashby [10]	0.62	0.48 §
Opsahl [7]		
Age group: 40-50	1.2	1.0
50-60	3.3	2.4
60-70	6.4	5.2

* This figure was not given by Pool but was obtained for the same population from Lord and McGrath.[9d]
† This figure was obtained from Hanf.[11l]
‡ This population consisted entirely of prison inmates.
§ These figures appear low, as they have been "weighted" by the authors to equate statistically the factor of age in the two groups.

group 2, which employ cancer death rates. The importance of method is now obvious.

Although using cancer death rates, the studies of group 2 are subject to another error. They are not based on autopsy confirmations. Even at a highly regarded general hospital, Wells[12] found that 36 per cent of fatal malignant tumors were not

10. Rudolph, G. DeM., and Ashby, W. R.: J. Ment. Sc. **80**:223, 1934.

11. (*a*) Pool.[9e] (*b*) Lord and McGrath.[9d] (*c*) Hahnemann.[6] (*d*) Büel, E. S.: Allg. Ztschr. Psychiat. **80**:312, 1925. (*e*) Warren, S., and Canavan, M. M.: New England J. Med. **210**:739, 1934. (*f*) Chevens.[3] (*g*) Lucksch, F.: Schweiz. med. Wchnschr. **76**:135, 1946. (*h*) Copeman, S. M., and Greenwood, M.: Great Britain Ministry of Health Report, No. 36, 1926. (*i*) Rudolph and Ashby.[10] (*j*) Opsahl.[7] (*k*) Report of the Board of Control of the Commission of Lunacy for England and Wales for 1909; cited by Lord and McGrath.[9d] (*l*) Hanf, D., cited by Warren and Canavan.[11e]

12. Wells, H. G.: Relation of Clinical to Necropsy Diagnosis in Cancer and Value of Existing Cancer Statistics, J. A. M. A. **80**:737 (March 17) 1923.

diagnosed until autopsy. With psychotic patients the clinical diagnosis is notoriously more difficult. Experience in preparing this paper indicated that nearly half the fatal malignant tumors had not been discovered clinically. Thus, cancer death rates based on clinical diagnoses alone are prone to a high degree of inaccuracy.

At the Worcester State Hospital figures were available to determine the cancer death rate on the basis of autopsy findings. As noted, the conclusions of White, Lewis, Chevens and Neubürger discussed above are based on proportionate mortality rates. Since their conclusions have become accepted almost as axiomatic, critical reevaluation by cancer death rates is indicated. It also was felt desirable to obtain figures on the incidence of cancer in some of the other diagnostic categories of psychoses and to investigate Lewis' conclusion that cancer is rare in patients with the "regressive" type of psychosis.

METHODS

The records of patients who died at the Worcester State Hospital from 1928 to 1942 were reviewed. Cases of malignant tumors occurring as follows were excluded: (1) cases of nonpsychotic patients (about 50); (2) cases in which the malignant tumor was an "incidental" finding, not contributing to death (six), and cases of "cure" by therapy, the investigation thus being based on cancer deaths, and not on the total incidence of cancer; (3) cases in which the malignant tumor was considered primary and an etiological factor in the psychosis (about 75). The last group was comprised of (*a*) cases of intracranial tumor and (*b*) cases in which the diagnosis was "psychosis with somatic disease."

The same exclusions were made for the population "still living." Remaining, as a basis for this study, were a computed series of 295 cases of death from malignant tumor, in 144 of which autopsy was performed, and 55,000 patient years (number of patients times period of hospitalization).

The following considerations governed the handling of the data:

1. It was determined that this hospital is representative of psychiatric hospitals in Massachusetts. The correlation of the uncorrected cancer rates for this hospital and for all Massachusetts psychiatric hospitals was 1.0. It was shown that cancer per se does not bring about selective admission (except as noted later) or discharge of patients. Four patients transferred for treatment of cancer were later returned to this hospital.

2. A correction was applied such that rates are approximated to what they would have been had autopsy been done in all cases of death. First, it was shown statistically that the cases were not selected for autopsy on the basis of age, diagnosis or the presence of cancer. Then, in each subgroup studied, the number of known cases of cancer was determined in which autopsy was not performed. Finally the number of cancers per 100 deaths which were not recognized clinically was determined. This percentage was applied to the group without autopsy. The two figures thus obtained were then added to the number of cancers found at autopsy. This computation was made for each group studied.

3. To eliminate the important effect of the duration of hospitalization on the cancer rates, all rates were computed annually for the period of the study and then expressed as means for the period. The number of patients "still living" was computed by adding the number still in residence and half the number discharged and on visit or parole for each year.

4. All statistics for psychotic patients and cancer deaths in psychotic patients were excluded from the Massachusetts general population figures.

5. In cognizance of the sharp increase in cancer rates with age, the results were expressed as age-specific cancer rates, or as expected cancer rates, so that exact age distribution could be accounted for.

6. The cancer death rates for Massachusetts were corrected in an effort to avoid the error introduced by mortality statistics which are not based on autopsy findings. Several investigators

have published detailed studies of this error. Estimates of the percentage by which mortality statistics must be increased to be accurate are as follows: De Vries,[13] 13.3 per cent; Riechelmann,[14] 13.78 per cent; Bilz,[15] 32.6 per cent, and Wells,[12] 36 per cent. In this study the cancer death rates for Massachusetts were increased by 30 per cent. This figure is not incompatible with the 50 per cent increase in rate for the nonautopsied patients or the 20 per cent difference resulting from difficulty in diagnosis of psychotic patients because of such factors as their uncooperativeness and unreliability in reporting the history and symptoms.

7. The data were not corrected for sex. In the general population of Massachusetts during the period studied, there was a slightly higher cancer death rate in the female population. Since the Worcester State Hospital population contained a slightly higher proportion of males, correction of the data for sex would have slightly increased the cancer death rates of the psychotic population.

RESULTS

Incidence of Malignant Tumors by Pathological Type.—This information is recorded in detail in other papers [16] and will be only summarized here. There was a remarkable agreement in the frequency of nearly every type of lesion in the present series with the reports for the general populations of Massachusetts and the United States.[9b] This suggests that the pathological type and situation do not differ in the psychotic and the nonpsychotic population. One interesting exception, reported previously,[9d] was an unusually high incidence of carcinoma of the pancreas in schizophrenic patients. (In both studies the data utilized preceded the general use of insulin therapy; so this could not be regarded as a possible causative factor.) There was no evidence that any endocrine abnormalities associated with psychosis manifest themselves in an unusual incidence of malignant tumors.

Opsahl [7] reported a high incidence of carcinoma of the stomach. In the present series there was a suggestively high incidence, but the difference between the psychotic and the nonpsychotic patient was not statistically significant. Malignant tumors of the structures derived from stoma and cloaca were of expected frequency.

Cancer Death Rates of the Psychotic Population as a Whole.—The cancer death rate rises sharply with age in both the psychotic and the nonpsychotic population (table 2). To allow for exact age distribution, expected cancer death rates by age are utilized in this study. For the psychotic population, the cancer rates were as follows:

	No. of Cancers per Annum
Expected number	13.3
Actual number	17.4

The difference is significant at far beyond the 1 per cent level of confidence. The same difference apparently holds for all Massachusetts psychiatric hospitals.[17] Had the exclusions listed under "Methods" not been made, the actual number would

13. de Vries, W. M.: Surg., Gynec. & Obst. **44** (Cancer Supp.) : 233, 1927.

14. Riechelmann, W.: Berl. klin. Wchnschr. **39**:728, 1902.

15. Bilz, cited by de Vries.[13]

16. Hahnemann.[6] Pool.[9c] Warren and Canavan.[11c]

17. Although the corrections described were not made for other Massachusetts psychiatric hospitals, the crude cancer death rates for these were almost identical with those of the Worcester State Hospital (Annual Reports of Massachusetts Department of Mental Health, 1929-1940).

have been about 22.0 per annum, an even greater difference. The opinion that cancer is rare in psychiatric hospital patients, relatively or absolutely, does not seem justified.[18]

Table 2 shows the striking difference in death rates from all causes between the two populations, psychotic and general. The use of proportionate mortality rates (8.1 per cent for this hospital; 13.0 per cent for Massachusetts) would have given the deceptive impression that cancer is less common in the psychotic population.

As in the general population, the cancer death rates of the psychotic population are increasing. There was an increase of 8.6 per cent for this hospital and of about 8.0 per cent for all psychiatric hospitals in the United States between 1925 and 1935. This observation is in contrast to the conclusion of Pool.[9c]

Distribution of Cancer Death Rates and General Death Rates by Age.—Table 2 shows that the cancer death rate was significantly higher in the psychotic population of this hospital than in the nonpsychotic population of Massachusetts at each age between 45 and 84. Although these differences are real, it will be shown that their

TABLE 2.—*Mean Annual Age-Specific Cancer Death Rates and Death Rates of all Psychotic Patients in the Worcester State Hospital, as Compared with Those of the Nonpsychotic Population of Massachusetts in 1930* *

Age Group	Worcester State Hospital		Massachusetts Nonpsychotic Population	
	Death Rate	Cancer Rate	Death Rate	Cancer Rate
25-34	21.1	0.0	3	0.2
35-44	24.5	1.5	5	0.8
45-54	42.3	4.1	11	2.5
55-64	86.5	7.1	23	5.8
65-74	182.5	15.2	51	11.0
75-84	457.8	25.5	125	15.9
85-99		31.0		29.0

* All differences in cancer rates between the ages of 35 and 84 are significant at better than the 5 per cent level. In the age groups 25 to 34 and 85 to 99 the differences are not significant.

meaning must be interpreted with caution because (1) at the ages of 35 to 64 there is an unexpected distribution of cancer in paranoid patients and (2) at the ages of 65 to 84 the difference is due to a high incidence of cancer associated with the psychoses of old age, in which special factors affect the cancer incidence.

Cancer Death Rates in the Population with "Chronic" Psychoses.—At this point it is imperative to determine the effect of cancer on the development of a psychosis or the rate of admission to a psychiatric hospital. The anemia, cachexia, operative procedures and other factors associated with malignant disease might well produce a psychosis or aggravate an existing one and lead to institutionalization. When this was recognized, the diagnosis "Psychosis with Other Somatic Disease" was made. Such cases were excluded from this study. Cases of this type, when unrecognized, however, might heavily weight the data. To evaluate this factor, the cancer death rates of the population with "chronic" psychosis were studied. It was assumed that any patient hospitalized more than two years did not have an advanced, unrecognized malignant tumor on admission. For the group "senile psychosis" this assumption was found to be unwarranted. This point becomes crucial and will

18. The absolute values of this paper may not be applicable to other states, since Massachusetts generally has both the highest psychotic admission rate and the highest cancer death rate in the general population.

receive separate discussion. In the group "psychosis with cerebral arteriosclerosis," 78 per cent of the cancer deaths occurred within two years of admission. In the other groups, however, this was not the case, and the cancer death rates were actually slightly higher for patients hospitalized more than two years, and in fact, more than five years. Thus, only in the psychoses with old age did cancer per se influence significantly the development of a psychosis or admission to a psychiatric hospital. If the psychoses of old age are excluded, the cancer death rates of the psychotic population are no longer higher than those of the general population.

Cancer Death Rates (and Death Rates) by Type of Psychosis.—Table 3 shows that the higher cancer death rate in the psychotic population is due to the high incidence of cancer in the psychoses with senility and cerebral arteriosclerosis. In

TABLE 3.—*Cancer Death Rates (and Death Rates) per 1,000 for Principal Types of Psychosis in Worcester State Hospital**

Type of Psychosis	Expected Cancer Death Rate †	Actual Cancer Death Rate	Critical Ratio ‡	Death Rate
"Exogenous psychoses"				
Senile psychosis	15.7	22.0	3.8 (H. S.)	339.0
Psychosis with cerebral arteriosclerosis	11.5	17.6	3.8 (H. S.)	356.0
Psychosis with cerebral syphilis	3.2	4.6	1.5 (N. S.)	140.0
Psychosis with mental deficiency	2.9	2.7	0.3 (N. S.)	27.0
Total	7.6	11.2	6.8 (H. S.)	214.0
"Endogenous Psychoses"				
Schizophrenia, all types	3.5	4.2	1.4 (N. S.) §	27.0
Paranoid types	3.5	9.9	6.5 (H. S.)	32.0
Hebephrenic and catatonic types	2.0	2.5	2.0 (P. S.)	25.0
Paranoid conditions	6.2	10.1	2.0 (P. S.)	33.0
Manic-depressive and involutional psychoses ‖	4.8	3.8	2.8 (S.)	56.0
Total	3.8	4.4	1.2 (N. S.)	31.0
Psychosis with chronic alcoholism	5.5	6.5	0.7 (N. S.)	49.0
Grand total—all groups studied	4.8	6.7	5.3 (H. S.)	81.0

* Certain groups, such as "psychosis with psychopathic personality" and "psychosis with epilepsy," were too small for inclusion, but are included in the totals.

† The "expected cancer death rate" is the rate that would be expected in this group on the basis of its age distribution if it had the same cancer rate as the general population of Massachusetts in 1930.

‡ A critical ratio of less than 2.0 equals a P of 0.05 and is not significant (N. S.). A critical ratio of 2.6 ($P = 0.01$) would indicate one chance in a hundred that the result is due to chance. In this study a critical ratio of 2.0 to 2.6 is considered probably significant (P. S.); a critical ratio of 2.6 to 3.0, as significant (S.), and a critical ratio of 3.0 or more, as highly significant (H. S.).

§ The class "schizophrenia, all types," is not simply the total of the "paranoid types" and the "hebephrenic and catatonic types," but includes the simple and the schizo-affective types, which are excluded from the table because the groups are too small for statistical significance. This explains the lack of significance of the difference between the expected and the actual cancer death rates in the group "schizophrenia, all types."

‖ The manic-depressive and involutional psychoses groups are combined to make the group statistically significant.

the "functional," or "endogenous," psychoses the cancer death rate does not differ significantly from that of the general population. The group "psychosis with cerebral arteriosclerosis" shows a cancer death rate of 17.6, but exclusion of all patients dying within two years of admission reduces this rate to 8.4. This figure is significantly less than the expected rate. In no other group is the cancer death rate altered in accordance with duration of hospitalization. This difference must be due to either or both of the following factors: (1) failure to distinguish clinically between cases of psychosis with cerebral arteriosclerosis and those with advanced malignant growth, and (2) aggravation of the psychosis with cerebral arteriosclerosis

by a malignant process. Experience indicates that both factors operate. In several cases with clinical pictures typical of cerebral arteriosclerosis autopsy showed little cerebral arteriosclerosis but revealed an unexpected malignant tumor. It would seem that this differential diagnosis warrants more attention. In addition to the clinical resemblance of the malignant tumor to a psychosis with cerebral arteriosclerosis, it is probable that the anemia or debility of advanced malignant disease aggravates an existing psychosis. It is postulated that in the presence of narrowed cerebral vessels even a mild decrease in stroke volume or hemoglobin may seriously increase cerebral anoxia.

The data do not bear out the impression that "carcinoma is a great rarity in cerebral arteriosclerosis."[5]

The senile psychoses show a high cancer death rate (table 3), which remains the same after exclusion of patients hospitalized less than two years, and, in fact, after exclusion of those hospitalized less than five years. It would appear, then, that the high incidence is not the result of the admission of patients already suffering from advanced malignant disease. The figure, however, is questionable because of the existence of factors that do not operate in any other group studied. In the senile group 52 per cent of the malignant tumors were epitheliomas of the face or carcinomas of the breast, and in patients hospitalized over five years 90 per cent of the tumors were of these types. Many of these patients, owing to the long course of tumors of these types, had been under treatment before admission. In this group, then, the influence of the malignant tumor on the psychosis could not be assessed. Were cases of this type excluded, the cancer death rate of the senile psychoses would virtually equal the expected rate.

In addition, the presence of cancer in senile patients may result in their admission to this hospital, whereas if they had been physically well they would have entered an old age home or a poor farm. Moreover, relatively few autopsies are performed on the noninstitutionalized aged over 85; so the expected cancer rate in this age group may be much underestimated.

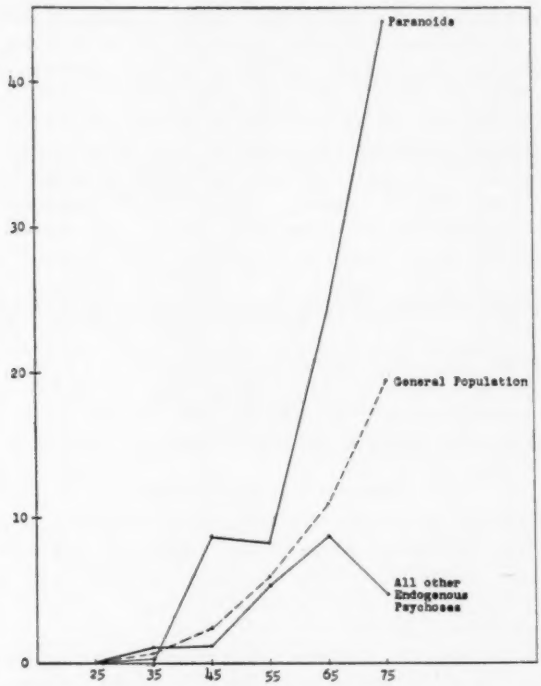
The true incidence, then, of malignant tumors in persons with a senile psychosis has not been determined. Although it is evident that institutionalized senile patients have a higher incidence of cancer than an equivalent noninstitutionalized group, the difference is adventitious and does not seem to evidence a greater susceptibility of patients with senile psychosis to malignant tumors. In this study, then, cancer death rates of the senile group are of crucial importance. Omission of the doubtful group "senile psychoses" and of the patients in the group "psychoses with cerebral arteriosclerosis" who had advanced malignant growths on admission so reduces the cancer death rates for the psychiatric hospital patients that the actual and the expected rates become equal.

In summary, the cancer death rate of the institutionalized psychotic population is greater than that of an equivalent nonpsychotic population, but this is probably due to selective admission rather than to a difference between the two groups in their susceptibility to malignant neoplasms.

The higher cancer death rates for the younger patients, aged 45 to 64, however, remain unexplained. In the groups with psychoses with cerebral arteriosclerosis and senility, nearly all of the patients were over 65 years of age. The patients under

64 belonged to categories of psychoses which, as a whole, had the same cancer death rate as the general population. The explanation of this discrepancy reveals an interesting phenomenon.

The accompanying chart shows that the cancer death rates in the groups "paranoid schizophrenia" and "paranoid conditions" are strikingly higher than the expected rates at all ages. The cancer death rate for the paranoid psychoses at ages 45 to 54 is four times, and that at ages 55 to 64 twice, the expected cancer death rate. The high cancer death rate of the psychotic population in the age groups of 45 to 64 is, then, due to the high incidence of cancer in young paranoid patients.



Comparison of cancer death rates by age for all paranoid psychoses, for all other endogenous psychoses, and for the Massachusetts general population in 1930.

The higher cancer death rates for paranoid psychoses are shown in table 3. The differences between actual and expected cancer death rates for these paranoid psychoses (when combined) is statistically highly significant. The observations of Lewis on paranoid schizophrenia are confirmed and extended to paranoid conditions. Collectively, the data of table 3 and the chart allow the further conclusion that cancer not only is more frequent, but is prone to occur in patients with the paranoid reaction types at an earlier age.

Dr. N. Kline has suggested an explanation for the high cancer death rate in paranoid patients. Sheldon's finding in regard to mesomorphic body habitus and

malignant tumors has been mentioned above. Recently Kline and Tenney [19] found a high incidence of mesomorphy in the patients with chronic paranoia. He suggests that the high incidence of mesomorphy in paranoid patients may explain in part the high cancer death rate of this group.

In comparing two populations by means of proportionate mortality rates, validity improves as the death rates (from all causes) approach each other. For patients with paranoid psychoses the death rates are not much higher than those for an equivalent general population. In paranoid psychoses, for which the cancer incidence is high, its frequency is revealed by proportionate mortality rates.

The low cancer rate in the hebephrenic and catatonic group is probably significant. This, too, tends to confirm Lewis' observations. In addition, it is of considerable interest that there is a low cancer death rate in the group with "manic-depressive and involutional psychoses." In the groups of the schizo-affective type of schizophrenia and the depressive types of senile psychosis there were insufficient cases for statistical validity, but the cancer death rates appeared low. These findings may indicate that cancer is relatively infrequent in the affective psychoses.

The cancer death rates for schizophrenia are increased by the high proportion of paranoid types. The low incidence of cancer for schizophrenia, reported by Chevens [3] and Hahnemann,[6] is considered the result of the method—use of proportionate mortality rates—which they employed. The findings in the present study agree with those of Opsahl.[7] The finding that the cancer death rate for psychoses with mental deficiency is equal to the expected rate is in agreement with Chevens.[3]

Table 3 shows that the higher incidence of cancer in the psychotic population is due to the high cancer death rates in the groups "senile psychosis" and "psychosis with cerebral arteriosclerosis." The high incidence for paranoid reaction types is "canceled out" by a low incidence for other "endogenous" psychoses.

SUMMARY AND CONCLUSIONS

The literature on cancer frequency in psychotic patients is reviewed. Some highly interesting observations are mentioned. These are considered to warrant reevaluation and elaboration. Results are conflicting because of confusion about statistical methods. The methodology considered proper for this type of investigation is outlined and explained.

The records of all psychotic patients and of patients with proved cases of cancer at the Worcester State Hospital between 1928 and 1942 were studied.

Pathologically, the distribution of malignant tumors did not differ in type or situation from those of the general population, except for a suggestive, but not significant, increase of carcinomas of the pancreas in schizophrenic patients.

In the psychotic population cancer was significantly more frequent than in the "control" population. The difference is due to the high incidence in the groups "psychosis with cerebral arteriosclerosis" and "senile psychosis." A study of "chronic" hospital patients shows that in these diagnostic groups (and in these alone) many patients are admitted who already have advanced cancer. When these groups are omitted, no real difference in cancer death rates appears between the psychotic and the nonpsychotic population.

19. Kline, N., and Tenney, A. M.: Am. J. Psychiat. **107**:5, 1950.

In patients with the other types of psychosis cancer does not cause a psychosis or lead to admission with significant frequency.

Between 1928 and 1942 cancer death rates increased in the psychotic population as they did in the general population.

In the groups "psychosis with mental deficiency," "psychosis with cerebral syphilis," "psychosis with chronic alcoholism" and "schizophrenia," cancer occurred with expected frequency.

With the catatonic, hebephrenic and schizo-affective types of schizophrenia, cancer was probably less frequent than expected.

With paranoid schizophrenia and paranoid conditions, cancer death rates were abnormally high. In addition, paranoid patients die of cancer at an unexpectedly early age.

Apparently, cancer is relatively rare in psychoses characterized by depressive reactions.

Cancer in the psychiatric hospital population is significantly commoner than in the general population. However there is no real difference between psychotic and nonpsychotic patients as a whole in their susceptibility to malignant disease.

Dr. David Rothschild and Dr. Nathan Kline gave helpful criticism in the preparation of this paper.

USE OF METHYLPHENYLSUCCINIMIDE IN TREATMENT OF PETIT MAL EPILEPSY

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NEW YORK

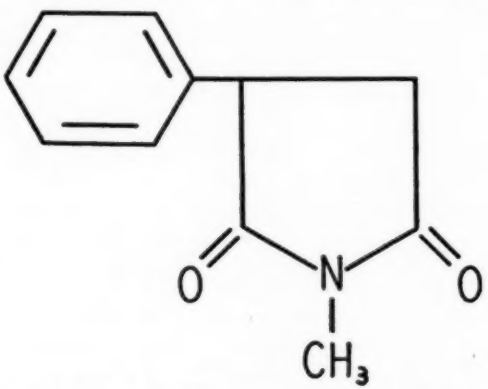
WHILE comparatively excellent drugs are available for the control or reduction of grand mal seizures, the agents which are used in the treatment of intractable petit mal attacks are often inadequate. Although bromides are now little used, heavy reliance still rests on the barbiturates, phenobarbital, and mephobarbital (mebaral®) and in recent years on the new drug trimethadione (tridione®).

Sedation, barbiturate rashes, and slowing of the mental processes are obvious disadvantages of the phenobarbital derivatives, while photophobia, drug rash, and leukopenia handicap the usefulness of trimethadione.

The compound (N-methyl-α-phenylsuccinimide [1]) which is discussed in this presentation has been found to equal or to surpass trimethadione in therapeutic efficacy and, in addition, is relatively nontoxic.

PHARMACOLOGY

N-methyl-α-phenylsuccinimide [2] has the following chemical structure:



In laboratory and clinical tests N-methyl-α-phenylsuccinimide has been designated as PM 334 and will hereinafter be so designated for the sake of brevity.

From the Department Neurology, Division of Child Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute, Presbyterian Hospital.

1. Parke, Davis & Company's trademark for this compound is milontin.®

2. This compound was developed in the Research Laboratories of Parke, Davis & Company, Detroit. Material for this study was forwarded to us through the courtesy of the Department of Clinical Investigation.

PM 334 was selected for chemical trial from a large number of drugs tested for their protective action against metrazol®-induced convulsions in animals. A dose of 125 mg. per kilogram of body weight was effective in protecting rats against the convulsant action of pentylenetetrazole U. S. P. (metrazol®). This dose is considerably smaller than that (500 mg. per kilogram) of trimethadione, suggesting an effectiveness, gram for gram, of four times in favor of PM 334.

Toxicity studies indicated that PM 334 was well tolerated by dogs when administered perorally five days a week for six to seven weeks in divided doses of 10, 20, and 40 mg. per kilogram of body weight daily. Biochemical, hematologic, and urinary findings remained in the normal range. PM 334 is also a relatively nontoxic substance when administered to mice perorally. When administered to mice in the diet ration, a daily dose of 1.0 to 1.5 gm. per kilogram of body weight produced no toxic reactions, and there was a normal gain in body weight. The blood and urine determinations on the patients reported here likewise gave normal values for the period of three to six months covered by this study. All blood and urine determinations on a larger group of patients receiving various other succinimide compounds for a period of months likewise gave normal values.

CLASSIFICATION OF ATTACKS

The classification of petit mal is complicated by the fact that petit mal attacks are not always easily distinguishable clinically from other forms of minor seizures. The electroencephalogram also is not infallible because the spike and wave complex, indicative of petit mal, may appear in the electroencephalogram of a patient whose clinical seizures are always of the grand mal type. Furthermore, a patient may have what appears to be clinically a petit mal pattern without confirmation of this in an electroencephalographic study.

In the face of this dilemma, as the investigation developed, it was thought best to devise a purely pragmatic scheme of classification based on direct clinical observation. Since petit mal and other types of seizures not infrequently occur in the same patient, and since a patient subject to epilepsy may have only petit mal at one point in his life and later only grand mal or some other type of seizure, it was felt that the cases studied should be divided into three groups according to the clinical type.

1. Pure petit mal (pyknolepsy)—that form of epilepsy which manifests itself in transient loss of consciousness only, with no concomitant motor phenomena.

2. Mixed petit mal—that form of epilepsy which manifests itself predominantly in transient loss of consciousness and minor motor phenomena.

3. Petit mal combined with other types of seizures.

It is recognized that this form of classification may penalize the data, since Group 2 includes not only the akinetic and myoclonic types of petit mal, as classified by Lennox,[3] but various nondeterminate forms as well. However, the scheme is believed justifiable and should serve to focus attention on the development of drugs which will prove effective in the large body of cases of petit mal so frequently seen by the general practitioner.

3. Lennox, W. G.: Tridione in the Treatment of Epilepsy, J.A.M.A. **134**:138 (May 10) 1947.

MATERIALS AND METHODS

This preliminary report is based on a study of 50 cases of petit mal selected in the Vanderbilt Clinic and the Division of Child Neurology of the Neurological Institute. The cases chiefly sought were those in which the seizures were intractable to standard anticonvulsant drugs, those with toxic responses to such drugs or cases characterized by both states.

While electroencephalographic confirmation of the clinical diagnosis was always sought, cases fulfilling the recognized clinical criteria of petit mal were not discarded when the spike and wave complex was absent.

The number of attacks was recorded by the parents on a daily calendar chart, and these data were transcribed to a duplicate chart for graphing when the patient returned to the clinic. It was believed that this method would provide a more acurate method of evaluating a drug than reliance upon the approximations of a parent based purely on memory.

Across the top of the chart, at the head of vertical columns, appeared the names of the three common types of epilepsy—petit mal, grand mal, and psychomotor. Calendar days from 1 to 31 were printed in the vertical column down the left-hand side of the chart. On the extreme right-hand side of the sheet sufficient room was left for marginal notes, and here explicit directions for dosage were written out. At the upper right-hand corner of the sheet was a list of the epileptic categories previously described.

TABLE 1.—*Previous Medication*

Drug	No. of Cases	Drug	No. of Cases
Phenobarbital	27	Sodium bromide	1
Tridione®	13	Phenurone® *	1
Mesantoin®	8	Paradione® †	1
Glutamic acid	6	Dilantin®	20
Mebaral®	2	No medication	2

* Phenacemide.
† Paramethadione.

RESULTS

Table 1 reveals that in only two of the 50 cases studied was there no history of previous medication.

In the remainder of the cases medication ran the entire gamut of anticonvulsant drugs, with phenobarbital still heading the list in frequency of use, followed by diphenylhydantoin and trimethadione. In the majority of instances indifferent success attended the use of these drugs in this series of cases. These facts, in our opinion, point up not only the need for more efficient drugs in the control of petit mal, but the much greater need for a wider armamentarium of more efficient drugs. Drugs which are efficient in one type of petit mal may be indifferently successful in another.

Table 2 demonstrates the average reduction in number of attacks, in terms of chronological continuity, under treatment with PM 334. In 15 patients, or 30% of the total number, the attacks were completely controlled; i. e., the patients were continuously free from attacks for at least four weeks, the average seizure-free period for the group being 12 wk. The range of complete control was from 4 to 31 wk. on an average daily dose of 2.4 gm.

Practical control is defined here as shown by that group of patients with a reduction in number of attacks ranging from 80 to 99% of the original, pre-experimental number. Fifteen patients, or 30% of the total, showed this range of

reduction in attacks. This group showed an average reduction in attacks of 90% below the preexperimental frequency for 13 wk. The average dose administered to accomplish this effect was correspondingly as high (2.4 gm.) as that in the group with completely controlled attacks.

Sixteen patients, or 32% of the total case load, showed a reduction in petit mal attacks ranging from 5 to 79%. The average reduction in attacks was 50%, or one-half the preexperimental frequency for a period of 13 wk. The average dose required to accomplish this was 2.3 gm.

Four patients, or 8% of the case load, were not helped at all over a period averaging 7 wk.

Ninety-two per cent of the total group showed a reduction in attacks with the use of PM 334. Sixty per cent of the group, representing complete control and

TABLE 2.—*Average Reduction in Attacks in Chronological Continuity*

	No. of Cases	% of Total Cases	Average % Reduction	Average Time of Reduction, Wk.	Average Daily Dose of PM 334, Gm.
Complete control	15	30	100	12	2.4
Practical control (80-99%)	15	30	90	13	2.4
Partial control (5-79%)	16	32	50	13	2.3
No effect	4	8	0	7	2.0
	50				

TABLE 3.—*Effect of PM 334 on Petit Mal Attack in Patients with More Than One Type of Seizure*

	Petit Mal		Mixed Petit Mal		Petit and Grand Mal		Petit Mal and Psychomotor Epilepsy	
	No.	%	No.	%	No.	%	No.	%
Complete control	7	24	3	50	4	31	1	50
75% or more reduction	13	44	2	33	4	31	..	..
Some reduction	7	24	..	..	4	31	1	50
No effect	1	4	1	17	1	7	..	..
Condition worse	1	4	..	..	..	..	..	..
Total	29		6		13		2	

practical control of seizures, showed a reduction ranging from 80 to 100% of the original number of attacks.

When the data are divided according to the type of attack (Table 3) as classified here, it will be seen that seven patients, or 24% of those with pure petit mal attacks; three patients, or 50% of those with mixed petit mal attacks, and four patients, or 31% of those with grand mal and petit mal combined, had their petit mal attacks completely controlled. One patient with petit mal and psychomotor attacks combined likewise had the petit mal attacks completely controlled.

Thirteen of a total of 29 patients whose seizures were diagnosed as pure petit mal, or 44%, showed a reduction in attacks of 75% or more. Two of the six patients with mixed petit mal likewise showed a reduction in attacks amounting to 75% or more below the preexperimental number. Four, or 31% of the total number with combined grand and petit mal, likewise showed a reduction of 75%

or more in the attacks. Seven, or 24%, of the patients with pure petit mal showed a reduction in attacks of 74% or less. Four, or 31%, of the 13 patients with combined grand and petit mal likewise fell in the same category. One patient with combined petit mal and psychomotor epilepsy also showed some reduction in attacks. The one patient in each of the diagnostic categories other than combined petit mal and psychomotor epilepsy showed no improvement. One patient with pure petit mal appeared to be made worse.

Table 4 shows the average number of attacks a week before treatment. Fifteen patients in whom complete control was obtained with PM 334 had a pretreatment average of 57 attacks a week. Nineteen patients in whom 75% or better reduction resulted had 123 attacks prior to treatment, or more than twice as many attacks as the group whose seizures were completely controlled by PM 334. In the 12 cases in which some reduction was secured, the average for pretreatment attacks was highest, namely, 170 per week, or almost three times the number found in the group with completely controlled seizures. No effect was obtained in 4 patients whose incidence of attacks before therapy was very small (13 a week).

The figures for the completely controlled, practically controlled, and partially controlled categories seem logical, inasmuch as the best results were secured with

TABLE 4.—*Data Divided According to Number of Attacks Before Treatment*

	No. of Cases	Average No. of Attacks a Week Before Treatment
Complete control	15	57
75% reduction	19	123
Some reduction	12	170
No effect	4	13
	50	

PM 334 when the pretreatment attack averages was lowest, the effectiveness of the drug being less apparent as the number of pretreatment attacks increased. This would seem to indicate a relation between the lower incidence of attacks prior to treatment and the effectiveness of the drug. Results in the four cases in which no effect was obtained seem to contradict this hypothesis, however, although the number of cases in that classification is so small as to make valid interpretation difficult.

DOSAGE

The average daily dose used in this series of cases was 2.4 gm., in units of 0.3 gm. capsules, or eight capsules a day. The range of effective dosage varies considerably; hence as much as 3 gm. per day (or 10 capsules) has been required to produce the maximal effect. There was very little relation in this series between dosage and age. As much as 1.5 gm. daily was given to a 6-mo.-old infant to produce the maximal effect, and as little as 0.9 gm. was the optimal dose for an adult. A number of patients received 3 gm. a day with no ill effects. The maximal daily dose given with no ill effects was 4 gm., in one case.

The usual practice in this series was to begin with 0.3 gm. three times a day and increase the dose by 0.3 or 0.6 gm. each week until the average daily dose of 2.4 gm. was reached. If the attacks were not controlled, and toxic signs did not

appear, the amount was increased at weekly intervals until 3 gm. per day was being taken, or the maximal effect was obtained. Since the toxic signs as a rule are not serious, the dose can be increased with some confidence. If toxic effects supervened, nausea and dizziness being the commonest, tolerance could often be improved by either reducing the dose somewhat or discontinuing it for a short period and then increasing it at a slower rate.

TOXIC SIGNS

Toxic signs of whatever nature appeared in 11 cases, or 22%, of the series. This is in marked contrast to the toxic signs in 55% of cases reported for trimethadione.[3] The toxic signs with PM 334 are also much less disturbing than those most commonly seen with trimethadione, such as photophobia and rash. Table 5 shows the toxic signs in terms of frequency and type.

Nausea and dizziness most frequently occurred together. Nausea occurred in one case with a dose of 0.6 gm. and did not appear in another case until 4 gm. daily was ingested. There is little or no relation in this series of cases between the size of the dose and the appearance of the toxic signs. The toxic signs appear to be based on individual idiosyncrasy to the drug. The number of cases is too few to justify exclusion of the possibility that an allergic cutaneous rash may

TABLE 5.—*Toxic Signs*

Type	Frequency, No. of Cases	Type	Frequency, No. of Cases
Nausea	4	Vomiting	1
Dizziness	4	Headache	1
Drowsiness	3	Dreamlike state	1

develop in some cases. It is also possible that some other untoward side effect may develop with long-continued use.

The blood and urine, as previously stated, were entirely normal throughout this experiment, covering many months, and with related succinimide compounds they remained normal over two years.

SUMMARY

The data show that N-methyl-α-phenylsuccinimide (PM 334) is equal to, if not superior to, trimethadione (tridione®) in therapeutic efficacy in the group studied and has the advantage of being relatively nontoxic. Animal tests likewise indicate that PM 334 is much more active than trimethadione. In our experience, N-methyl-α-phenylsuccinimide has also proved more efficacious in that group of cases in which standard medicaments gave only indifferent to fair results.

Complete control of seizures was obtained for a period of from four to 31 wk., with an average of 12 wk. for the group, in 30% of the total case load on an average daily dose of 2.4 gm. Practical control was secured in 30% of the cases, this group showing an average reduction in attacks of 90% below the preexperimental frequency for 13 wk. Thirty-two per cent of the total case load showed an average reduction in attacks of 50%, while only 8% of the entire group was not helped at all over an average period of seven weeks.

The average daily dose required to produce the maximal effect in this series was 2.4 gm., in units of 0.3 gm. capsules, or eight capsules a day. The range of effectiveness of the dose varies considerably, however, and as much as 3 gm. a day, or 10 capsules, had to be used in some cases to obtain the best effect. There was very little relation in the series between dose and age. When data are divided according to type of attack, dose, or age, no pattern emerges which indicates a direct relation between any of these factors and the effectiveness of N-methyl-α-phenylsuccinimide.

There is also little or no relation in this series of cases between size of the dose and the appearance of toxic signs. Toxic signs are much less disturbing than those most commonly seen with trimethadione and are less frequent. Listed in order of frequency, the toxic signs produced by PM 334 are nausea, dizziness, drowsiness, vomiting, headache, and a dreamlike state, appearing in 22% of the cases studied. The toxic signs which do appear seem to be based on individual idiosyncrasy to the drug. The number of cases is too few to justify exclusion of the possibility that an allergic cutaneous rash may develop in some cases. It is also possible that some other untoward side effect may develop with long-continued use.

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EFFECTS OF ADMINISTRATION OF THE ADRENOCORTICOTROPIC HORMONE (ACTH) ON PATIENTS WITH MYASTHENIA GRAVIS

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IN VIEW of the small number of patients with myasthenia gravis and the risk of administration of pituitary adrenocorticotropic hormone (ACTH) to these patients, a report of observations on the effect of administration of this drug to a relatively large group of patients with myasthenia gravis seemed justifiable.

Administration of ACTH to patients with myasthenia gravis was first begun in 1944 by Torda and Wolff.[1] A partial remission, consisting essentially in the patient's ability to perform more work while taking significantly reduced amounts of neostigmine bromide, resulted from administration of the hormone. ACTH became commercially available in 1948, and confirmation of the first observations was subsequently reported.[2]

MATERIAL AND METHODS

Subject Material.—The effect of ACTH was studied in 15 patients. The series comprised men and women of ages from 18 to 61 yr. who had had myasthenia gravis from one to 17 yr. The patients were mildly to severely ill. The severity of the symptoms was appraised by

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1. Torda, C., and Wolff, H. G.: Effect of Adrenotrophic Hormone of Pituitary Gland on Ability of Tissue to Synthesize Acetylcholine, Proc. Soc. Exper. Biol. & Med. **57**:137-139, 1944.

2. (*a*) Torda, C., and Wolff, H. G.: Effects of Adrenocorticotrophic Hormone on Neuromuscular Function in Patients with Myasthenia Gravis, Proc. Soc. Exper. Biol. & Med. **71**:432-435, 1949; (*b*) Effects of Adrenocorticotrophic Hormone on Neuromuscular Function in Patients with Myasthenia Gravis, J. Clin. Invest. **28**:1228-1235, 1949; (*c*) Effects of Adrenocorticotrophic Hormone of the Pituitary Gland on Neuromuscular Function in Patients with Myasthenia Gravis, Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, pp. 575-587. (*d*) Soffer, L. J.; Gabrilove, J. L.; Laqueur, H. P.; Volterra, M.; Jacobs, M. D., and Sussman, M. L.: The Effects of Anterior Pituitary Adrenocorticotrophic Hormone (ACTH) in Myasthenia Gravis with Tumor of the Thymus, J. Mt. Sinai Hosp. **15**:73-80, 1948. (*e*) Kane, C. A.: Recent Advances in the Medical Therapy of Myasthenia Gravis, read before the Twenty-Third Postgraduate (New York Academy of Medicine) Fortnight Clinic, Veterans Administration Hospital, New York, Oct. 18, 1950.

(1) clinical observations, (2) electromyographic recordings, and (3) biochemical studies, consisting of determination of the ability of blood serum to support acetylcholine synthesis. A summary of the clinical state of the patients is given in Table 1.

During the two years before this special study the patients either showed progression of the disease or had experienced minor, transient, but not significant changes in their clinical state.

Plan of Study.—The patients were permitted to take known amounts of neostigmine bromide and, if already receiving them, other known amounts of medicaments. On the patient's admission to the hospital, electromyographic studies and acetylcholine synthesis determinations were performed once a day approximately at the same time of the day. After a one-week period of

TABLE 1.—*Summary of Clinical State of Patien*

Patient	Sex	Date of Hospitalization	Age, Yr.	Duration of Disease, Yr.	Severity of Disease	Thymectomy	X-Ray Treatment of Thymus	Patient Bedridden	Lid Ptosis	Diplopia	Chewing, Swallowing	Muscle Fatigability	Neostigmine Bromide, Mg./Day
Gn	F	11/48	45	10	S*	—	+	+	+	+	S	S	180
Ls	F	3/49	24	4	S	—	+	+	+	+	S	S	450
		3/50						—	—	—			
		11/50						—	—	—			
Et	F	12/49	18	2	S	—	—	+	+	+	Mo.	S	450
		5/50						—	+	Occ.	Mo.	Mo.	360
								+	+	+	Mo.	S	225 6 mg. inj.
Kr	F	1/50	29	16	S	—	—						
		2/50						+	Occ.	+	Mi.	Mo.	120
		5/50						+	Occ.	Occ.	—	Mi.	120
Fg	M	12/49	39	11½	Mo.	—	—	—	+	+	Mo.	Mo.	300
		6/50						—	Occ.	+	Mi.	Mo.	150
Yh	F	3/49	31	9	Mo.	+	—	—	+	+	S	Mo.	150
								—	Occ.	Occ.	Mi.	Mi.	90
So	F	4/49	37	13	Mo.	—	+	—	+	+	Mo.	Mo.	120
Si	M	1/50	61	2	Mo.	—	—	—	+	+	Mi.	Mi.	225
Li	F	2/50	24	3	Mo.	—	—	—	—	—	Mo.	Mi.	120
Rn	F	6/49	29	17	Mi.	—	+	—	+	+	Mi.	Mi.	60
Fo	F	2/50	26	11½	Mi.	—	+	—	+	+	Mi.	Mi.	75
Br	F	1/50	30	10	Mi.	—	—	—	Occ.	Occ.	—	Mi.	90
Mn	M	9/50	22	1½	Mi.	—	—	—	+	Occ.	Mi.	Mi.	90
St	M	2/50	44	1	?§	—	—	—	+	Occ.	Mi.	Mi.	0
Gy	F	11/50	42	8	?‖	—	—	—	+	+	Mi.	Mi.	90

* S indicates severe; Occ., occasional; Mo., moderate, and Mi. mild.
† Eph. is ephedrine and guan., guanidine.
‡ Prosector's note: "In a number of sections of muscle only one area of lymphorrhagia can be found. There are only a few remnants of thymus."
§ Diagnosis, hyperthyroidism.
‖ Diagnosis, muscle dystrophy.

observation each patient received 25 mg. of ACTH every six hours for five days. Tests were performed during the administration of the hormone, after two weeks of the last injection of ACTH, after one month, and occasionally thereafter. After administration of ACTH the intake of neostigmine bromide, as well as that of other medicaments, was regulated according to the needs of the patient.

Electromyographic Recording.—The electromyograms were taken according to a previously described method [2a,b] from the muscles of the hypothenar eminence during stimulation of the ulnar nerve with stimuli of 10 and 30 pulses per second, each of 100-μ sec. during and of "supramaximal" intensity, for two minutes.

Electromyograms were recorded usually for seven days before administration of ACTH and at biweekly intervals thereafter for two months. The records were taken at the same time of

the day, three hours after administration of neostigmine bromide before and during administration of ACTH, and from 6 to 15 hr. after administration of neostigmine bromide after completion of the series of injections of ACTH. In patients mildly ill with myasthenia gravis the records were taken 12 hr. after the last administration of neostigmine bromide.

Acetylcholine Synthesis.—Acetylcholine synthesis in the presence of blood serum was studied according to the method described by Torda and Wolff.[3] The method consists of incubation of a choline acetylase and a substrate-containing tissue with blood serum and determination of the amount of acetylcholine formed during the period of incubation. The ability of serum to support acetylcholine synthesis was tested before, during, and after administration of ACTH.

ts Before and After Administration of ACTH

			Symptoms, Two Wk. After Administration of ACTH									
Other Medications †	Drop in Action Potential, % of Control	Drop in Acetylcholine Synthesis, % of Control	Patient Bedridden	Lid Ptosis	Diplopia	Chewing, Swallowing	Muscle Fatigability	Neostigmine Bromide Mg./Day	Other Medications	Drop in Action Potential, % of Control	Decrease in Acetylcholine Synthesis, % of Control	Died
K; eph.	75	55	—	Occ.*	+	Mo.*	Mo.	90	K; eph.	6	2	—
K; guan.; eph.	68	50	—	—	—	Mi.*	Mi.	45	Guan.; eph.	4	4	—
Eph.	20	19	—	—	—	—	Mi.	45	Guan.; eph.	3	2	—
Eph.	7	2	—	—	—	—	—	45	Guan.; eph.	2	0	—
None	65	50	—	Occ.	Occ.	Mo.	Mo.	180	None	10	8	—
None	50	40	—	—	—	Mi.	Mo.	180	None	8	10	—
K; guan.; eph.	56	45	+	Occ.	+	Mi.	Mo.	120	K; guan.; eph.	25	20	—
Same	30	20	+	Occ.	Occ.	Mi.	Mo.	120	Same	12	10	—
Same	12	6	—	—	Occ.	—	Mi.	120	Same	8	7	—
None	39	40	—	—	Occ.	—	Occ.	60	None	3	0	—
None	18	15	—	—	—	—	—	30	None	5	3	—
None	40	42	—	Occ.	Occ.	Mi.	Mi.	30	None	5	2	—
None	10	6	—	—	—	—	—	0	None	3	0	—
None	33	40	—	—	Occ.	Mi.	Mi.	15-0	None	4	3	—
None	20	20	..	....	..	....	....	..	.....	..	..	3d day‡
None	10	8	—	Occ.	Occ.	Mi.	Mo.	60	None	8	6	—
Eph.	15	15	—	—	—	—	—	45-0	Eph.	3	0	—
None	10	6	—	—	Occ.	Mi.	Mi.	45	None	4	3	—
None	10	10	—	—	—	—	—	0	None	3	1	—
None	13	8	—	Occ.	Occ.	Mi.	Mi.	60	None	2	0	—
None	8	5	—	—	Occ.	—	Mi.	0	None	6	4	—
None	0	0	—	—	+	—	—	90	None	0	0	—

OBSERVATIONS

Control Subjects.—Under the same experimental condition as that of the patients, and without administration of neostigmine bromide, healthy subjects maintained unaltered the amplitude of the muscle action potential during repetitive indirect stimulation with 10 pulses per second for two minutes, and the amplitude of the action potential decreased an average of 12% during stimulation with 30 pulses per second for two minutes. Furthermore, the ability of blood serum to support acetylcholine synthesis was relatively stable, and the amount of acetylcholine synthesized at 38 C. by a frog brain mixture in the presence of blood serum averaged 1.45γ.[3]

3. Torda, C., and Wolff, H. G.: Effect of Blood Serum from Patients with Myasthenia Gravis on the Synthesis of Acetylcholine in Vitro, J. Clin. Invest. **23**:649-656, 1944.

Patients with Myasthenia Gravis Before Administration of ACTH.—The severely ill patients showed an average decrease of 75 to 40% in the amplitude of the muscle action potential during a 30-sec. period of stimulation with 10 pulses per second (Fig. 1; Table 1) and a decrease in ability to support acetylcholine synthesis of from 55 to 40 per cent (Table 2). They were bedridden on a daily intake of neostigmine bromide of from 240 to 450 mg. (Table 1).

The moderately ill patients showed an average decrease of from 40 to 15% in the ability to maintain the amplitude of the muscle action potential (Fig. 1; Table 1) and a decrease in ability to support acetylcholine synthesis of from 40 to 15% (Table 2). On a daily intake of neostigmine bromide of from 90 to 240 mg. they were grossly incapacitated (Table 1).

The patients who were mildly ill with myasthenia gravis showed less than a 15% decrease in ability to maintain the muscle action potential (Fig. 1; Table 1).

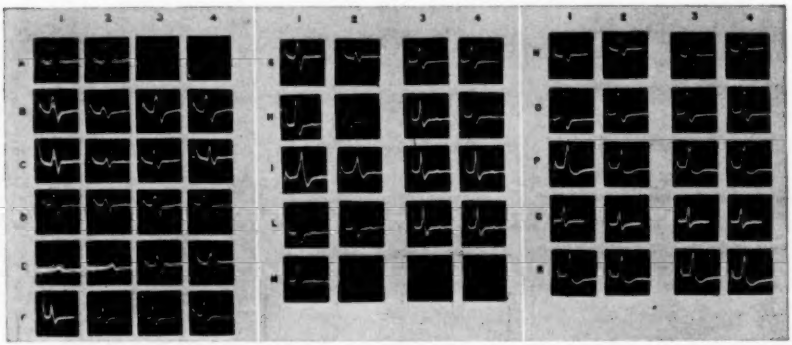

Fig. 1.—Effect of ACTH on muscle action potential during repetitive indirect stimulation at a frequency of 10 pulses per second (percutaneous stimulation of the ulnar nerve).

Columns *1* represent action potential records taken at the beginning of the 30-sec. stimulation period with a stimulus of a frequency of 10 pulses per second. Columns *2* represent records taken at the end of the 30-sec. stimulation period without moving the electrodes.

The records in columns *3* and *4* were taken the third day after administration of ACTH. By that time the intake of neostigmine bromide was reduced, and not three hours, but from six to 15 hr., elapsed between the last intake of neostigmine bromide and the recording of the action potential.

Columns *3* represent records taken at the beginnings of the 30-sec. stimulation period with a stimulus of a frequency of 10 pulses per second, and columns *4* represent records taken at the end of the 30-sec. stimulation period without moving the electrodes.

Row *A* represents records taken from a healthy control subject. The amplitude of the muscle action potential was maintained unaltered during the stimulation period.

Row *B* was taken from patient La; row *C*, from Yh; row *D*, from So; row *E*, from Gn; row *F*, from Rn; row *G*, from Et; row *H*, from Kr; row *I*, from Fg; row *L*, from Li; row *M*, from Si; row *N*, from Gy; row *O*, from Mn; row *P*, from Br; row *Q*, from Fo; row *R*, from St. Before administration of ACTH the amplitude of the muscle action potential decreased significantly within the first few pulses of stimulation in most instances, the degree depending on the severity of the patient's symptoms, and was maintained at this level thereafter. After administration of ACTH the amplitude of the action potential was maintained unaltered in all instances, similarly to healthy persons.

They supported acetylcholine synthesis within normal limits (Table 2), and on a daily intake of neostigmine bromide of from 45 to 90 mg. they showed only mild fatigability (Table 1).

During the First Administration of ACTH.—During the last two days of administration of ACTH and for a few days thereafter, a gradually increased disability occurred, consisting mainly of asthenia, malaise, headache, insomnia, and in some instances dyspnea. One patient with "bulbar" manifestations died on the third day of administration of ACTH. Assuming that in patients with moderately severe myasthenia gravis of a few years' duration the muscles contain areas of lymphorrhagia and the thymus is hyperfunctioning, it may be of significance with regard to the usefulness of ACTH in treatment of myasthenia gravis that autopsy in this case showed but one area of lymphorrhagia in a number of sections of muscle and only a few remnants of thymus.

The severity of the symptoms during administration of ACTH seemed to be reduced by the concurrent administration of from 3 to 5 gm. of potassium chloride by mouth during the period of administration of ACTH and for one day thereafter.

During administration of ACTH the electromyogram and the ability of blood serum to support acetylcholine synthesis gradually increased and approximated normal values on the fifth day of administration of the drug.

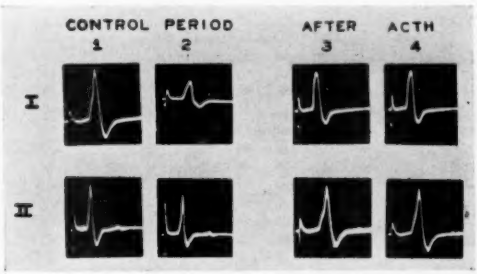

Fig. 2.—Effect of administration of ACTH in two instances on the muscle action potential of a patient originally severely ill with myasthenia gravis during repetitive indirect stimulation at a frequency of 10 pulses per second (percutaneous stimulation of the ulnar nerve).

Column *1* represents action potential records of a patient taken at the beginnings of the 30-sec. stimulation period with a stimulus of a frequency of 10 pulses per second. Column *2* represents records taken at the end of the 30-sec. stimulation period without moving the electrodes.

The records in columns *3* and *4* were taken the third day after administration of ACTH. By that time the intake of neostigmine bromide was reduced, and not three, but 15 hr. elapsed between the last intake of neostigmine bromide and the recording of the action potential.

Column *3* represents records taken at the beginnings of the 30-sec. stimulation period with a stimulus of 10 pulses per second, and column 4 represents records taken at the end of a 30-sec. stimulation period without moving the electrodes.

Row *I* represents records of patient Ls, severely ill before administration of ACTH, taken before and after the first series of administration of ACTH.

Row *II* represents records of patient Ls before and after the second series of administrations of ACTH.

After Administration of ACTH.—General Observations: When improvement in the clinical state of the patient occurred, it began during the first week after the last injection of ACTH and continued for a few weeks. In most instances the patient exhibited a significant partial remission, consisting in increased well-being, increased work performance on a reduced intake of neostigmine bromide, and a decreased requirement of neostigmine bromide. Amounts of neostigmine bromide

required for maintenance of the patients before administration of ACTH induced symptoms of curarization. Four patients were able to omit use of neostigmine bromide completely. Sensitivity to guanidine increased somewhat. A summary of the clinical state of the patients is given in Table 1. Remission occurred both in patients not receiving potassium chloride and in patients receiving potassium chloride during administration of ACTH. Patients Li, Fo, Mn, and St failed to demonstrate convincing evidence of remission.

To date a complete relapse to the degree of severity of symptoms existing before administration of ACTH has not occurred in any of the 14 patients. Two patients showed a partial relapse after severe infections, and one, after a severe psychological shock.

Electromyography: The ability to maintain the amplitude of muscle action potential during repetitive stimulation with frequencies of 10 and 30 pulses per second returned within normal limits in all instances (Fig. 1).

TABLE 2.—*Effect of ACTH on Ability of Blood Serum to Support Acetylcholine Synthesis*

	Amount of Acetylcholine Synthesized, in per Cent of Control Value														
	Patient														
Experiment	Gn	Ls	Et	Kr	Fg	Yh	So	Sl	Ll	Rn	Fo	Br	Mn	St	Gy
Before first ACTH.....	45	50	50	55	60	58	60	80	92	80	94	90	92	95	100
Third day of ACTH.....	92	98	92	93	94	97	100	..	98	99	96	95	96	97	99
Few days after ACTH.....	94	96	95	97	99	98	97	..	99	95	97	100	95	99	98
Three months after ACTH...	92	95	93	..	95	96	96	..	..	99	98	96	95	96	97
Second Series of ACTH															
Before first ACTH.....	..	81	60	80	85	94	..	..	..	..	..	..	..	..	..
Third day of ACTH.....	..	99	95	98	97	100	..	..	..	..	..	..	..	..	..
Few days after ACTH.....	..	100	90	100	100	100	..	..	..	..	..	..	..	..	..
Three months after ACTH...	..	97	..	..	99	99	..	..	..	..	..	..	..	..	..
Third Series of ACTH															
Before first ACTH.....	..	94	..	94	..	..	..	..	..	..	..	..	..	..	..
Third day of ACTH.....	..	96	..	97	..	..	..	..	..	..	..	..	..	..	..
Few days after ACTH.....	..	99	..	100	..	..	..	..	..	..	..	..	..	..	..

Acetylcholine Synthesis: The ability of the blood serum to support acetylcholine synthesis returned within normal limits (Table 2).

During and After Administration of a Second and Third Series of ACTH.—Achievement of another or a more complete remission by a second and a third series of administration of ACTH was also attempted. The time elapsed between the series of administrations of ACTH was from four weeks to 10 mo.

During administration of ACTH in amounts of 25 mg. every six hours for five days, an impairment of the clinical state of the patients was observed similar to that occurring during the first series of administration of the drug. The severity of the symptoms developed seemed to depend on the severity of the myasthenia gravis at the time immediately before administration of ACTH, and not on whether or not ACTH had been given before. Again, the adverse symptoms seemed to be reduced by simultaneous administration of potassium chloride.

Within a few days after the last administration of ACTH a new and significant remission was experienced.

When defects in performance of the muscle action potential and the acetylcholine synthesis occurred, these functions returned to normal during and after administration of ACTH (Fig. 2; Table 2).

Control Experiments.—To ascertain whether enthusiasm or suggestibility was partially responsible for the remissions of the patients receiving ACTH, some of the severely ill patients (Ay, Ls, Pl, Rr) and moderately ill patients (Yh, Kr, Rn, So) received intramuscular injections of various placebos before or without receiving ACTH. The placebos were saline solution, denaturated ACTH, denaturated whole pituitary extract, testosterone, diluted desoxycorticosterone acetate, oxidized glutathione, and procaine. The placebos did not modify the ability of the blood serum of the patient to support acetylcholine synthesis, the ability to maintain the amplitude of muscle action potentials unaltered during repetitive stimulation, or the clinical state of the patient.

THEORY OF ACTION OF ACTH ON PATIENTS WITH MYASTHENIA GRAVIS

Present evidence supports the view that the immediate cause of the symptoms of patients with myasthenia gravis is a decrease in the synthesis of acetylcholine.[3] There is a close relation between the ability of nerve to maintain good function during repetitive stimulation and an adequate supply of acetylcholine.[4] Both maintenance of the action potential and ability to support acetylcholine synthesis are impaired in patients with myasthenia gravis, and to a degree paralleling the severity of clinical symptoms.

ACTH seemingly has a specific effect on the mechanism responsible for the symptoms of myasthenia gravis by increasing the synthesis of acetylcholine and by restoring to normal the impaired ability to maintain the amplitude of the action potential during repetitive stimulation.[5] The effect of ACTH on the nerve is due not to a direct fixation of the hormone on choline acetylase [4b] but to an indirect mechanism involving an increase in the intracellular concentration of substances that augment the activity of choline acetylase.[6] These effects of ACTH cannot be duplicated fully by cortisone.[4c]

GENERAL COMMENT

The present report confirms and elaborates the previously reported results [2a-c] on a larger series of patients with myasthenia gravis. Pituitary adrenocorticotropic hormone (ACTH) induced a significant partial remission of the symptoms in a majority of patients. This remission was long-lasting in the sense that, although the patients may have lost in the ensuing three or four months some of what they had initially gained, they did not relapse to the former level. A remission is, by the nature of the disorder, incomplete, since structural changes in muscle occur after disuse of a few years' duration. Even assuming that regeneration under suit-

4. (*a*) Torda, C., and Wolff, H. G.: Effects of Hypophysectomy and Adrenocorticotrophic Hormone on Neuromuscular Function and Acetylcholine Synthesis, Am. J. Physiol. **161**:534-539, 1950; (*b*) Effect of Hypophysectomy and Adrenocorticotrophic Hormone (ACTH) on Acetylcholine Metabolism and Neuromuscular Function, J. Pharmacol. & Exper. Therap. **98**:32, 1950; (*c*) Effect of Pituitary and Adrenocortical Hormones on Neuromuscular Function, Am. J. Physiol. **164**:755 (Dec.) 1950; (*d*) ibid., to be published; (*e*) Effect of 2-Methyl Naphthoquinone on the Action Potential of Nerve and Muscle, ibid. **158**:465-469, 1949; (*f*) footnotes 1 and 2 a-c.

5. Torda and Wolff, footnotes 1 and 4a, b, and c.

6. Torda, C., and Wolff, H. G.: Acetylcholine Synthesis, Science **103**:645-646, 1946, footnote 2a.

able conditions may ultimately take place, such regeneration would not exhibit itself in a short time.

There is good evidence for the view that changes occur at the myoneural level after administration of ACTH in patients showing decreased ability to support acetylcholine synthesis and decreased ability to maintain the amplitude of muscle action potential during repetitive stimulation before administration of ACTH. The recognition of improvement of the clinical state was usually easy in moderately to severely ill patients with myasthenia gravis but was difficult in mildly ill patients.

The administration of ACTH to patients with "bulbar" manifestations is fraught with danger, and the hazards must be fully appreciated before the hormone is administered.

The choice of 500 mg. of ACTH for each series of administrations is arbitrary and is based on the observation that 250 mg. induced only a fleeting clinical improvement. Since progressive improvement was observed during a few months after administration of ACTH, it was considered appropriate to wait at least two months before additional ACTH was given.

SUMMARY

Administration of 500 mg. of pituitary adrenocorticotropic hormone (ACTH) to 15 patients with myasthenia gravis induced in 10 a significant partial remission of long duration. Occurrence of remission could not be definitely established in four patients who were very mildly ill with myasthenia gravis.

During administration of ACTH most of the patients became weaker, and one patient died during the third day of administration of ACTH. The symptoms so developed seemed to be reduced in severity by the concurrent administration of potassium chloride.

New series of ACTH (500 mg. per series) induced further remission in all patients to whom it was administered.

TUMORS OF THE SPINAL CORD ASSOCIATED WITH CHOKING OF THE OPTIC DISKS

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BILATERAL choking of the optic disk has been demonstrated to be caused at times by high-lying tumors of the cervical portion of the spinal cord, particularly those that encroach on the foramen magnum. However, the development of choked disks secondary to tumors in the low thoracic, lumbar and sacral regions of the spinal cord has not been reported, so far as we know. In a brief review of the literature, we could not find any reported case in which choked optic disks were associated with a tumor of the spinal cord located below the second thoracic segment. In his recently published text, Walsh [1] does not mention any such case. Recently, one of us (J. G. L.) operated for tumor located low in the spinal cord on two patients in whom the clinical findings, and particularly the presence of bilateral choked disk, suggested, in addition to the lesion of the spinal cord, increased intracranial pressure resulting from a space-occupying intracranial lesion, such as a neoplasm of the brain. In neither instance, however, was any such intracranial lesion demonstrated. It seemed necessary to conclude, therefore, that the choked optic disks were caused by the tumor in the spinal cord. The rarity of such cases warrants this report.

REPORT OF CASES

CASE 1.—A boy aged 12 yr. was referred to the Mayo Clinic in March, 1949, because his local neurologist had found high-grade choking of both optic disks and a grossly yellow fluid on lumbar puncture. The cerebrospinal fluid coagulated as soon as it was exposed to air. A tentative diagnosis of "tumor of the posterior fossa" had been made by the referring neurologist. Furthermore, in a tentative diagnosis, it was stated that a congenital intracranial vascular lesion, probably an angioma or aneurysm, was the most likely pathologic process. The history was that of a boy who had not been well for the previous year and who complained of pain in both legs. The pain was greater on the left side than on the right. This was the patient's chief complaint. He had received the diagnoses of "rheumatic fever," "Perthes disease," and "sacroiliac and hip infection." He had been seen by several orthopedic surgeons because of his difficulty in walking and his complaint of pain in the legs. The boy had begun to gain weight about a year before coming to the Mayo Clinic. In September, 1948 he started to complain of pain in his eyes and blurred vision. About this time he began to have bilateral frontal headaches, and about February

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1. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, pp. 343-344.

1949 he began to have restless sleep. At this time he was seen by the referring neurologist, who discovered the bilateral choking of the optic disk and the strikingly xanthochromic cerebrospinal fluid.

Examination disclosed a rather obese boy 12 yr. old. There were marked spasm of the erector spinae muscles, some degree of scoliosis, and some shortening of the hamstring muscles. It was the shortening of the hamstring muscles which accounted for the unusual gait. Kernig and Lasègue signs were elicited bilaterally, being more pronounced on the left than on the right. Otherwise, the neurologic examination gave no objective abnormal signs; that is, there was no increase in the deep reflexes, no Babinski phenomenon, no weakness of any group of muscles or of any individual muscle, and no sensory loss.

Examination of the eyes revealed the ability to read 14/21 with each eye, with the proper correcting lenses. The movements of the external ocular muscles were normal. The pupils were normal. The visual fields were normal in the confrontation test. The media were clear. There was bilateral choking of the optic disk, with elevation of 4+ D. There were considerable exudation and hemorrhage on each disk. The retinal veins were engorged; a few hemorrhages were seen along the veins in the retina at some distance from the disk in each eye. There was no evidence of angiomatosis of the retina. The usual tests of the blood and urine gave normal results, and the flocculation test for syphilis was negative. Roentgenologic examination of the thorax disclosed nothing abnormal, but roentgenograms of the skull revealed separation of the sutures as a result of increased intracranial pressure. There was some degree of decalcification of the floor of the sella turcica. Roentgenologic examination of the spinal column revealed some degree of scoliosis in the lumbar region. The hip joints were normal. Erosion of the pedicles of the 12th thoracic and first and second lumbar vertebrae was seen, with enlargement of the spinal canal and thinning of the laminas at that level. The findings were considered consistent with the presence of an intraspinal tumor between the 12th thoracic vertebra and the upper border of the third lumbar vertebra.

Because we knew of no similar case in which increased intracranial pressure and choked optic disks had been caused by a tumor situated low in the spinal cord, we felt that what confronted us probably was a lesion of the spinal cord, possibly with intracranial implants, or that there might be a primary intracranial tumor with implants in the spinal cord. Because of the high degree of choking of the optic disks, it was deemed advisable to carry out a ventriculographic study before proceeding with operation on the spinal cord. Accordingly, on March 28, 1949, ventriculography was performed with the patient under the influence of a local anesthetic. Both lateral ventricles were tapped without difficulty. The ventricular fluid was grossly yellow and somewhat opalescent. In all, 110 cc. of fluid was removed from the ventricular system and was replaced with air. The air could be passed with ease from right to left and left to right through the third ventricle. The ventriculograms were excellent. They showed symmetric hydrocephalus, grade 3, of the lateral ventricles. The third ventricle was dilated, grade 3. There was no displacement or deformity. The aqueduct was dilated but not displaced. The fourth ventricle was well visualized; it did not appear to be displaced or deformed. There was air in the posterior cerebellar fossa and the upper cervical portion of the spinal canal, thus excluding the possibility of any obstructing lesion within the cranium or along the ventricular system. The total protein content of the fluid removed from the ventricular system was 180 mg. per 100 cc. There were 1 lymphocyte and many erythrocytes in a cubic millimeter of fluid. The result of the Kolmer test was negative; the colloidal gold curve was 0001110000. Because of the absence of any evidence of a space-occupying lesion within the cranium, it was advised that we proceed with attention to the spinal cord at the level of erosion of the vertebral pedicles and laminas.

Accordingly, on March 30, a needle was introduced successively at the fifth, fourth, and third lumbar interspaces, but no fluid could be obtained. At the second lumbar interspace a few drops of hemorrhagic, xanthochromic fluid were obtained. The fluid coagulated immediately. At the 12th thoracic space, a better flow of fluid was obtained, but there was a complete subarachnoid block. At the 11th thoracic space xanthochromic fluid and partially hemorrhagic fluid were obtained; there was no block at this space. During the Queckenstedt test the fluid rose in the manometer from 22 to 36 cm. on bilateral compression of the jugular vein.

Laminectomy was carried out immediately. It was started at the point of entrance of the upper needle, namely, the 11th thoracic space. A discolored dura mater was encountered. When

the dura mater was opened, an unusually large, tortuous vessel on the dorsal aspect of the cord was noted. The appearance of this vessel suggested an angioma, but we could not exclude the possibility that a solid tumor was situated below, pushing the conus and the lower part of the thoracic section of the cord upward and causing the enlargement of this vessel. Hence, laminectomy was extended downward. We came upon a huge tumor, which necessitated extending the laminectomy for a considerable distance. A specimen of the tumor tissue was sent to the pathologist, who reported it to be an ependymoma. At first it looked as though it were a part of the thoracic section of the cord, but it was hoped that it had taken its origin from the filum terminale and had extended up along the cord. This proved to be the case. The arachnoid was opened; as the tumor was gradually dissected, it was found that it could be freed from the thoracic portion of the spinal cord. Dissection was carried upward and downward until it became possible to shell out the entire tumor (Figure). The lower thoracic portion of the cord had been pushed upward and was very edematous. The conus medullaris and the right half of the cauda equina were displaced strongly to the right; the left half of the cauda equina was displaced to the left. After the main bulk of the tumor had been enucleated, we identified the filum terminale and dissected it well down below the lower end of the laminectomy area to the point at which it appeared normal. At this point the filum was silver-clipped and divided. It was then turned upward; a silk ligature was placed through the tip of the conus medullaris, and the tip of the conus, with the filum terminale and the attached tumor, was removed. The piece of conus medullaris which was submitted with the tumor to the pathologist

Ependymoma of the intradural portion of the filum terminale removed in case 1.

was found to contain tumor cells; hence, an additional 0.5 cm. of the conus was removed. This portion was reported by the pathologist to be free of tumor tissue. After all bleeding had been controlled, the dura mater was closed with a continuous stitch of black silk, and the wound was closed in layers without drainage. During the course of the operation 500 cc. of blood was administered. A postoperative roentgenogram of the spinal column revealed that the laminectomy extended to include the 11th and 12th thoracic and the first three lumbar vertebrae. The silver clip placed on the tip of the resected filum terminale and one on the resected conus medullaris could be seen. The silver clip on the resected conus was opposite the first lumbar vertebra. The pathologist reported the tumor as an ependymoma, grade 3, measuring 10 by 2 by 2 cm.

The patient's convalescence was normal except that his temperature rose to 101 or 102 F. and persisted at that height for approximately 10 days after the extensive laminectomy and removal of the neoplasm of the spinal cord. Sutures of the ventriculography wounds were removed on the third postoperative day, and those of the back were removed on the sixth postoperative day. Both wounds healed without incident. Lumbar puncture was carried out at intervals during the postoperative course, and hemorrhagic fluid was removed from the canal. Reexamination of the optic disks showed that the papilledema was receding. Neurologic reexamination after the operations revealed no major neurologic disturbance. The patient voided without difficulty, and there was no loss of sensation. The patient was dismissed and proceeded directly to his home on the 16th postoperative day.

The condition of this patient has been followed with much interest. He has been back on several occasions for reexamination. On June 9, approximately two months after removal of

the tumor of the spinal cord, roentgenologic examination of the head disclosed, in comparison with roentgenograms made on March 24, 1949, that there was less evidence of separation of sutures and that the decalcification of the floor of the sella turcica, which had been noted in the original roentgenograms of the head, was no longer present. Roentgenologic examination of the entire spinal column disclosed the residual effects of extensive laminectomy and erosion of the posterior aspects of the bodies of the upper three lumbar vertebrae. Some degree of scoliosis still was present. On June 10, vision was normal in both eyes, and the pupils, reflexes and visual fields also were normal. Ophthalmoscopic examination revealed residual gliosis in both optic disks. The lower poles of the disks were elevated 1 D., but there was no actual edema. The patient was myopic to the extent of about 3 D., and glasses were advised to correct this abnormality. On June 16 the basal metabolic rate was —18 per cent.

Examination of the eyes on December 1, eight months after the operation, showed the vision to be normal. The ocular fundi were normal, except for the presence on each optic disk of connective tissue residual to the previous papilledema. Orthopedic examination on Dec. 2, 1949, disclosed that there was still a list of the trunk to the right. There was low dorsal kyphosis. Roentgenograms exhibited the changes previously mentioned. A Taylor brace was adjusted to the patient's back, and he was advised to continue with exercises and to report back at the end of four months for reexamination.

Case 2.—A man aged 44 was operated on by one of us (J. G. L.) on Sept. 28, 1944, for an intramedullary glioma of the lower thoracic portion of the spinal cord. At that time his sensory level extended upward to the 12th thoracic dermatome. Subarachnoid block was not demonstrated at diagnostic lumbar puncture, although the cerebrospinal fluid contained 280 mg. of protein per 100 cc. Results of examination of the patient's eyes were entirely normal. There was no choking of the optic disks. The removed tumor was reported as being an oligodendroglioma.[2] The patient did well after that operation until late in 1949, when he began to lose the use of his lower extremities. His condition progressed, and locally an unsuccessful attempt was made to obtain cerebrospinal fluid. Arrangements were made to send the patient back to the Mayo Clinic for further consideration, since at the time of the operation in 1944 an opinion had been given that the patient probably would do well for several years, and that at the time of recurrence of the tumor in the spinal cord of sufficient extent to produce gross neurologic defect additional surgical treatment was to be considered. The patient had complained of considerable headache. Just before he was to leave his home to return to the clinic, it was discovered that he had bilateral choking of the optic disks. The patient was brought to the clinic by air, with his own bed.

Examination revealed paraplegia, with loss of motor and sensory function up to the ninth thoracic dermatome. Examination of the eyes disclosed bilateral choking of the optic disk, with elevation of 4½ to 5 D. on the right and 4 D. on the left. There was no defect in the visual fields except for greatly enlarged blindspots. Roentgenologic examination of the head revealed no abnormal changes. Because of the experience we had had in the previous case, it was felt that in the present instance the choking of the optic disks might well be secondary to recurrent tumor of the spinal cord or that it might be due to subarachnoid implants from that tumor.

The ventricular system was visualized by removing the fluid from the posterior cistern and replacing it with air. This fluid was grossly yellow and hemorrhagic and reminded me (J. G. L.) of the fluid which had been removed from the ventricular system in the previous case. The fluid was under increased pressure; it measured 29 cm. above the level of the posterior cistern with the patient in an upright chair. The ventriculogram made after the substitution of air for the fluid demonstrated slight dilatation of both lateral ventricles. There was no deformity. The fluid contained 160 mg. of protein per 100 cc., and 28,266 erythrocytes, 54 lymphocytes and 8 polymorphonuclear leukocytes, per cubic millimeter. The result of the Kolmer-Wassermann test was negative, and the colloidal gold curve was 0001110000. The air column opposite the upper part of the cervical region appeared to be displaced posteriorly. For

2. According to Bucy and Russell (Bucy, P. C., and Russell, J. R.: Oligodendroglioma of the Spinal Cord: Report of a Case, Arch. Neurol. & Psychiat. **63**:669 [April] 1950), only six cases of oligodendroglioma of the spinal cord had been reported prior to the report of their one case in April, 1950.

this reason, we could not be sure that there might not be a space-occupying lesion at the foramen magnum, or just below. In view of the choking of the optic disks and the fact that the patient had a recurrent tumor of the spinal cord which might not be relieved by surgical means, cervico-occipital exploration was carried out in order to exclude the possibility of a space-occupying lesion in the upper cervical region of the spinal column and in the posterior fossa and for purposes of decompression. The exploration revealed nothing abnormal except for thickening of the arachnoid, which on microscopic examination proved to be only a thickened, fibrous arachnoid. The wound was closed in layers as an exploratory decompression. Two days later laminectomy was carried out. At this time we found an extensive recurrence of the oligodendroglioma within the thoracic portion of the cord. In addition, there were two small subarachnoid hematomas, one just above and one just below the swollen section of the cord. Extensive removal of the intramedullary oligodendroglioma was carried out. At this operation, the dura mater was left wide open; otherwise, the wound was closed in layers and without drainage.

The patient's postoperative convalescence was uneventful, and the choking of the optic disks was receding at the time of his dismissal on May 21, 16 days after laminectomy and removal of the intramedullary tumor of the lower thoracic portion of the spinal cord. His headaches were relieved. There was little or no change in his neurologic status.

Comment on Cases 1 and 2.—Edema of the optic disks observed in patients who have lesions of the spinal cord is in most instances a manifestation of optic neuritis or axial retrobulbar neuritis with visible edema of the disks. In both the cases reported here, however, central vision was normal, and the fields of vision were normal, as determined by confrontation tests. In the second case, color vision was normal as tested on pseudoisochromatic charts, and on the tangent screen the only abnormality that could be demonstrated was enlargement of the physiologic blind-spots. The only possible ophthalmologic diagnosis, therefore, was simple papill-edema or "choked disks."

Although the exact mechanism of the development of choked optic disks is not known, their presence is generally accepted as evidence of an increase in intracranial pressure. They occur rather frequently in association with acquired internal hydrocephalus. The factor responsible for the development of choked optic disks in our two cases probably was the demonstrated internal hydrocephalus. Papilledema without primary loss of vision seems to be due occasionally to an increase in the protein content of the cerebrospinal fluid. But the protein content of the cerebrospinal fluid in these two cases, although increased (180 and 160 mg. per 100 cc., respectively), was hardly high enough to be adjudged responsible for the development of papilledema.

Except when secondary optic nerve atrophy develops, it is not usual for choked optic disks to recede unless the increased intracranial pressure is reduced definitely. In the first of our two cases, elevation of the disks was reduced appreciably within three weeks after the removal of the tumor of the spinal cord. Examination of the eyes eight months later revealed that the optic disks were flat and that there was no evidence of secondary optic nerve atrophy. By the time the second patient had left the hospital, the papilledema was receding definitely. The rather rapid recession of the choked disks in these cases suggests that the internal hydrocephalus and the resultant papilledema were secondary to a complete block in the circulation of the cerebrospinal fluid at the site of the tumor in the spinal cord.

In the course of follow-up study of 116 cases in which pathologically verified intramedullary tumors of the spinal cord and gliomas of the intradural filum terminale had been seen at the Mayo Clinic previous to 1940, 4 cases were found in

which the tumor was associated with choking of the optic disks. In three of these four cases, the choked optic disks may not have developed as a result of block of the cerebrospinal fluid produced by the tumor of the spinal cord. Arachnoidal implants were present in two cases and may be presumed to have been present intracranially. In the third case, although the tumor situated in the 12th thoracic segment of the spinal cord was an astrocytoma, grade 2, an unidentified lesion was present in the lung and may have been the source of intracranial metastasis. In retrospect, the fourth case was probably similar in type to the two cases which form the primary basis of this report.

Case 3.—A married woman aged 43 presented herself at the clinic on May 22, 1925, because of pain in the pelvis. She said, moreover, that she had "always" been subject to headaches. Twelve years before she came to the clinic, when she was 31, she had undergone hysteropexy, salpingectomy, "resection" of the ovaries, and appendectomy. The reason for performance of these procedures was not given, but thereafter she experienced pain low in the abdomen, which was fairly constant but which occurred with striking monthly exacerbations. At the age of 33 menstruation stopped. After this the monthly attacks of pain became worse and included the right lower extremity, the back, the neck (where it was especially severe), the temples, and the right ear. The pain was worst in the morning and was relieved somewhat by sitting up in bed. After three or four days it would subside. Four years before coming to the clinic, the patient had undergone another pelvic operation, in which adhesions were cut. This seemed to relieve the intensity of the attacks, but not the frequency, for subsequently they came every two or three days. However, her health improved, and during the year that preceded her registration she felt decidedly better. Four weeks before her registration at the clinic, however, she had an attack that was very severe, and three weeks before, another. In the course of this attack, she vomited, and for three or four minutes the fingers became numb and rigid and the thumbs rolled inward. When she awakened the next morning, she saw double, and her husband told her that her eyes were crossed. Thereafter she suffered about 12 more attacks.

The patient cooperated well in the examination. The lateral rectus muscle of each eye was almost completely paralyzed; there was well-marked nystagmus of the inturning eye when she looked toward the right or the left. Vision in each eye was 6/6. The fields of vision were grossly normal. Ophthalmoscopic examination disclosed bilateral acute choked optic disk with hemorrhages and exudation; the right optic disk was elevated from 3 to 4 D., and the left, 4 D. A sacral dimple was noted. Lasègue's sign was elicited, but only moderately. The patient was aware of a slight disturbance in sensation of the buttocks and the posterior aspects of the thighs. The rectal sphincter was weak; however, the perineum had been torn badly. The blood pressure was 180 mm. of mercury systolic and 120 mm. diastolic. The urine contained some leukocytes.

Lumbar puncture showed the pressure to be more than 30 cm. of water with the patient lying on her side; compression of the jugular vein was not reflected by movement in the column of fluid in the manometer; neither was coughing or straining. The fluid was bright yellow and contained a moderate number of erythrocytes. Cisternal puncture also demonstrated elevated pressure. The fluid obtained at cisternal puncture was pale yellow; approximately the same number of erythrocytes was present as in the fluid obtained by lumbar puncture. Search was made for malignant cells, but none were found. The ventricular fluid was clear and under increased pressure. It seemed probable that the case was one of a tumor situated low in the spinal canal associated with a concomitant disturbance intracranially in the posterior fossa, possibly metastatic implants.

Of these two pathologic processes, the lesion within the head seemed to be the more menacing. It was decided to carry out cerebellar exploration. On June 20, Dr. Adson did so and found the dura mater to be tense and bulging. Pressure on it caused pain low in the abdomen. The arachnoid was thickened, opalescent, and yellow-tinged, and the subarachnoid fluid was iridescent, as though cholesterol crystals were floating in it. A diagnosis of "leptomeningitis" was made. After operation vision improved, but the backache continued.

On July 2, 12 days after operation, the choking of the optic disks had receded to 1½ D. in the right eye and 2½ D. in the left eye. In the right eye, the edema extended into the peripapillary retina, and there was a partial macular star. Large hemorrhages were still present in the retinas. On July 6, four days later, further subsidence of the edema was noted; the right optic disk was elevated 1+ D., and the left, 2+ D. There was some pallor of the disks, suggesting commencing secondary optic atrophy. There were small hemorrhages in the periphery of each retina and a large hemorrhage temporal to the left disk, with adjacent edema and exudation.

On July 8 the iliopsoas muscles were somewhat weak; all muscles of the lower extremities were very weak; the triceps surae reflexes were almost absent, and moderate impairment of cutaneous sensation could be demonstrated over the buttocks and thighs. That same afternoon Dr. Adson performed laminectomy at the level of the third lumbar vertebra and discovered an ependymoma, verified pathologically, that continued upward within the spinal cord. The tumor was not explored beyond the ninth thoracic vertebra, and no attempt was made to remove it. X-ray therapy was given.

On July 22, 32 days after the cerebellar exploration, ophthalmoscopic examination revealed that the optic disks were pale, but not measurably edematous. Small hemorrhages and residua of edema were still present in the retinas, along with vascular changes secondary to the previous extensive edema.

On May 17, 1930, five years after these operations, the patient wrote that she could walk and work and had normal sensation and normal control of sphincters.

COMMENT

It is probable that in any patient who presents bilateral choked optic disk, along with neurologic changes diagnostic of a tumor of the spinal cord, it will always be necessary to exclude the possible presence of a separate intracranial lesion. However, the signs and course of events in the present group of patients seem to demonstrate that obstruction to the circulation of the cerebrospinal fluid sufficient in degree to cause choking of the optic disks can occur not only in the ventricular system but at any level in the spinal canal.

CLINICAL AND PATHOLOGICAL FINDINGS IN A CASE OF DYSTROPHIA MYOTONICA

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IN 1944 I [1] described a typical case of dystrophia myotonica in a man aged 44. Death occurred in 1948, and autopsy was performed. An anatomical examination was made of the endocrine glands, the muscles and the central and peripheral nervous systems.

CLINICAL FINDINGS

The patient was extremely bald; the left eye was artificial, and the right eye revealed the remains of iridectomy and an operation for cataract. He presented the characteristic aspect of the facies myopathica, and the general appearance was that of typical *Jammergestalt*. Speech was unintelligible; the thyroid gland was not palpable. There was fairly general adiposity. The left testis was very small; the right testis was still smaller, being about the size of a marble. Both were soft. There was male distribution of hair. The extremities were thin and showed atrophy of the muscles. The left leg was thinner than the right. The calves and the muscles of the lower arms were especially atrophic. In walking the patient turned his feet inward.

Neurological examination showed ptosis of both eyelids, and in shutting the eyes the left eye did not close completely. The patient could not wrinkle his forehead or grimace. He usually sat with his mouth open. Chvostek's sign was elicited on both sides. There was pronounced atrophy of the sternocleidomastoid muscles. The shoulders slouched, and the patient lacked the power to straighten them or to turn the head to right or left. If the head was drawn backward, he was unable to lift it again. There was no myotonia of the tongue. The upper and lower arms were much atrophied, and the right and left deltoids were equally masked. The hands hung bent at the wrists, and at the metacarpophalangeal joints the thumbs were adducted. The interosseus muscles were atrophied. Power in the hands was defective. When the fist was clenched, the patient could open his hands only very slowly; but when this movement was repeated, he became quicker and better at it. There was no passive myotonia when the biceps was tapped. The arms had very little power! The Achilles tendon reflex was absent on both sides. Flexion and extension of the knees were weak; the muscles of the back were also weak. Sensation was intact.

The patient was mentally defective and homosexual.

Laboratory studies revealed urobilinuria, decreased serum creatine (0.8 and 1 mg. per 100 cc.), a lowered nonionized, protein-fixed calcium level of the blood serum (8 mg. of free calcium ions and 1.6 mg. of fixed calcium per 100 cc.). The roentgenogram showed thickening of the bones of the skull.

First assistant to the Neurological Clinic, Wilhelminagasthuis.

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1. den Hartog Jager, W. A.: Over dystrophia myotonica, Psychiat. en neurol. bl., p. 1 (Jan.) 1944.

The urine contained estrogenic substances, 30 international units per liter (normal, 50 to 200 international units); androgens, less than 15 international units (normal, 35 to 45 international units), and gonadotropins, less than 20 international units.

The cerebrospinal fluid was normal.

Six brothers and sisters had all died young. They had all been mentally defective. A photograph showed a brother and sister with open mouth. The patient's mother and a sister and a brother of the mother had been operated on for "a film in front of both eyes."

AUTOPSY

The patient died of bronchopneumonia in April 1948. Autopsy, 24 hours after death, revealed pneumonia in the lower lobe of the right lung and a tuberculous cavity, as large as a bean, in the middle lobe. The pleura was thickened on the right side. The liver was small and weighed 1,225 Gm. The weight of the pancreas was 375 Gm.; that of the fresh brain, 1,250 Gm.; that of the fresh hypophysis, 0.75 Gm.

The brain was removed, together with the cervical and the highest part of the thoracic portions of the spinal cord. Macroscopically, nothing abnormal was found. Sections were obtained of the sciatic nerve, of the trunk and calf muscles, of the hypophysis, the testis, the thyroid gland, the parathyroid glands and the adrenal glands. Sections were also taken of the kidney and liver. Hematoxylin-eosin sections were made of the internal organs. Hematoxylin-eosin sections were also made of the spinal cord, and further staining was performed by the Nissl, Weigert-Pal and Bielschowsky methods.

The brain stem was cut in serial sections from the septum pellucidum as far as, and including, the nucleus ruber, and then from the pons to the spinal cord. Every tenth section was stained by the Nissl and Weigert-Pal methods. Furthermore, Nissl and Weigert-Pal stains were made of pieces of the thalamus, nucleus caudatus, globus pallidus, putamen, nucleus dentatus, paleocerebellum and neocerebellum, gyrus centralis anterior, gyrus frontalis superior, gyrus centralis posterior, gyrus parietalis inferior, gyrus temporalis medius and occipital pole.

General Microscopic Preparations.—Hypophysis: Examination was made according to the method described by Rasmussen.[2] For this, the hypophysis was cut horizontally in serial sections. Three sections were selected on the vertical axis at the one-fourth, one-half and three-fourths levels. Each fifth microscopic field in every fifth row of fields was counted, the sections having been prepared with the Mallory stain or some other stain which gave a clear differentiation of the basophil, eosinophil and chromophobe cells of the hypophysis. In this way, 10,000 to 30,000 cells were counted. If 20 to 30 sections were counted, the variation is only 2 per cent of the count of three sections, according to Rasmussen. This count thus represents the distribution of the three types of cells in the hypophysis of adult man. In the count on the hypophysis of 100 adult men who had had sudden accidental deaths and thus, presumably, had normal hypophyses, Rasmussen obtained the following values:

Cells	%
Eosinophil	22.6 — 59.9
Basophil	4.5 — 27.4
Chromophobe	34.0 — 65.9

The hypophysis in the case described was stained according to the duazor method of Ruyter[3]; the cell count was as follows:

	Level				
	One-Fourth	One-Half	Three-Fourths	Total	Percentage
Eosinophil	310	1,381	1,650	3,341	15.0
Basophil	3,335	4,005	563	7,903	35.5
Chromophobe	1,506	7,031	2,454	10,991	49.4

Thus there was an important increase in the number of basophil cells, and there was a considerable decrease in the number of eosinophil cells.

2. Rasmussen, A. T.: Percentage of Different Types of Cells in Male Adult Human Hypophysis, Am. J. Path. **5**:263 (May) 1929.

3. Ruyter, J. H. C.: A New Staining Method for the Hypophysis, Acta neerl. Morph., p. 180, 1943.

In addition, in this hypophysis a fairly large cyst had formed in the anterior lobe, which was visible to the naked eye and was filled with a substance which stained red (fig. 1). Scattered throughout the hypophysis were numbers of small cysts filled with colloid, which stained red. A strong infiltration of basophil cells could be seen in the posterior lobe (fig. 2). There also was an increase in the amount of connective tissue.

Testis (Fig. 3): The specific epithelium showed almost complete atrophy. The ducts were almost completely dehyalinized, and there was great proliferation of the interstitial cells.

Thyroid Gland: The gland exhibited one layer of cubical epithelium. The colloid spaces differed greatly in size, as is the case in goiter. The interstitial tissue was well developed.

Parathyroid Glands: Two kinds of cells are normally distinguishable and were seen in this sections, the so-called oxyphil cells, with small nuclei and closely packed chromatin, and cells with very light protoplasm and large nuclei of lighter color. Here and there was a hint of follicle formation, and even a distinct formation of lumens, the whole having a normal appearance.

Adrenal Glands: Of these structures only small pieces were available. It was easy to distinguish the glomerular zone, the fascicular zone, the reticular zone and the medulla. This picture and the individual cells were normal.

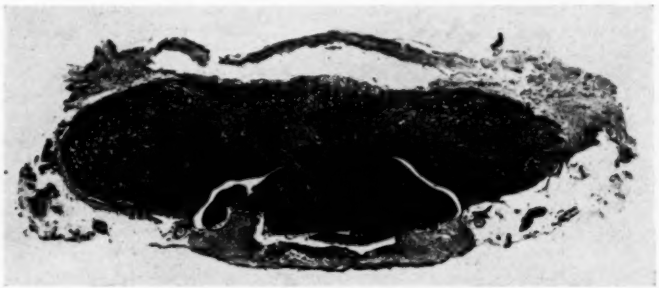

Fig. 1.—A large cyst in the anterior lobe of the hypophysis.

Kidneys: Examination showed an increase in cellular interstitial tissue and an increase in the nuclei of the glomeruli, as well as a deposit of brown pigment in the ducts. In many glomeruli there was proliferation of connective tissue on the inner side of the capsule, and the glomeruli were large. The picture was one of sclerosis of the glomeruli.

Liver: The sections presented an entirely normal picture.

Microscopic Preparations of the Nervous System and Muscles.—Spinal Cord: Only the cervical and the upper part of the thoracic portion of the spinal medulla were available for examination. In the Weigert-Pal sections diffuse demyelination was visible in the transverse sections of the anterior roots.

In the Nissl preparations the central canal was clearly visible. It was surrounded by glia cells, mostly on the anterior side. The picture was similar to that of a normal control preparation; the so-called glial *stick* of Sinnige and den Hartog is seen in normal sections of the spinal cord and is not pathological, as was described by these authors in their case. The motor cells of the anterior horn were pyknotic and shrunken. Several of the cells exhibited tigrolysis and clumping of the tigroid substance (fig. 4). In some of the large ganglion cells the neuron appeared to have become corkscrew shaped. Most ganglion cells were pear shaped. They were decreased in number. This was in contrast to the normal Nissl picture of the cells of Clarke's column.

Sciatic Nerve: Sections prepared with Bielschowsky and hematoxylin-eosin stains were normal (fig. 5).

Trunk Muscles: The hematoxylin-eosin stain showed an enormously increased number of nuclei (fig. 6). These nuclei lay in rows at the outer edge of the muscle fibers, as well as in the center. Some nuclei were long, rod-shaped, and others were rounder. The rod-shaped

nuclei lay end to end in long rows. The calf muscle (fig. 7) was much more abnormal. Between the muscle fibers here and there was connective tissue much richer in cells than normal. The muscle fibers still showed cross striations, but here, too, the nuclei lay in long rows and the rounder nuclei were gathered into closely packed nests.

Brain Stem: The hypothalamic nuclei from the septum pellucidum as far as, and including, the nucleus ruber (Nissl stain, nomenclature according to Clark [4]) are described.

Pars supraoptica hypothalami: This area extends from the anterior border of the chiasm to the tuber cinereum. It contains the nucleus paraventricularis and the nucleus supraopticus.

(*a*) Nucleus paraventricularis. This nucleus lay at a short distance from the right and left walls of the third ventricle. It was well developed and well vascularized. The nucleus could be followed through 130 of the serial sections. The cells frequently exhibited a circular accumulation of tigroid substance in the periphery. The nucleus of the cell also often lay at the periphery, which is its normal position (Clarke). A few cells appeared to be of a vague, frothy structure,

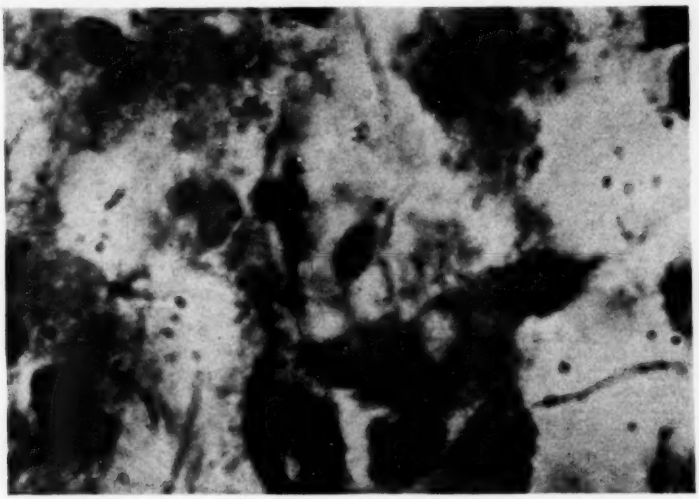

Fig. 2.—Basophil cell infiltration of the posterior lobe of the hypophysis.

but the great majority of them could be described as normal. (*b*) Nucleus supraopticus. The cells were of the same type as those of the nucleus paraventricularis. Here, too, the Nissl granules and the nucleus of the cell lay in a peripheral position, as they do normally. The nucleus consisted of comparatively closely packed cells, and all the cells were so sharply circumscribed and so well developed as to be distinguishable with the naked eye in the Nissl sections. This was true for the lateral portion of the nucleus, which lies lateral to the optic chiasm. The medial portion of this nucleus, which lies near the medial part of the optic tract, was also well developed. A few degenerated cells could be seen. Some cells exhibited neuronophagia and satellitosis. The great majority of these were normal.

Pars tuberalis: Behind the optic chiasm lies the pars tuberalis of the hypothalamus. It contains the nucleus hypothalamicus dorsomedialis and the nucleus hypothalamicus ventromedialis. These nuclei consist of small cells and lie beneath and behind the posterior portion of the nucleus paraventricularis.

4. Clark, W. E. Le Gros; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects, The Henderson Trust Lectures, nos. XIII-XVI, published for the William Ramsay Henderson Trust, Edinburgh, Oliver & Boyd, 1938.

Nucleus hypothalamicus posterior: This area lies farther back, where the pars tuberalis hypothalami borders on the pars mamillaris hypothalami. Histological study of this area revealed the following picture:

(*a*) Nucleus hypothalamicus ventromedialis. This nucleus consisted of closely packed, rather small cells, light in color, and was very distinct and quite normal in appearance.

(*b*) Nucleus hypothalamicus dorsomedialis. This nucleus was less sharply outlined and could hardly be termed well defined. Here the cells also showed a normal Nissl picture.

(*c*) Nucleus hypothalamicus posterior. This nucleus was formed of cells of the same type as the nucleus supraopticus and nucleus paraventricularis. The nucleus could be seen on anteroposterior vertical sections to lie between the wall of the ventricle and the fornix in sections in which the corpus mammillare began to develop. The cells were less closely packed, however, than in the other two nuclei described, and the structure of the protoplasm was finer, although

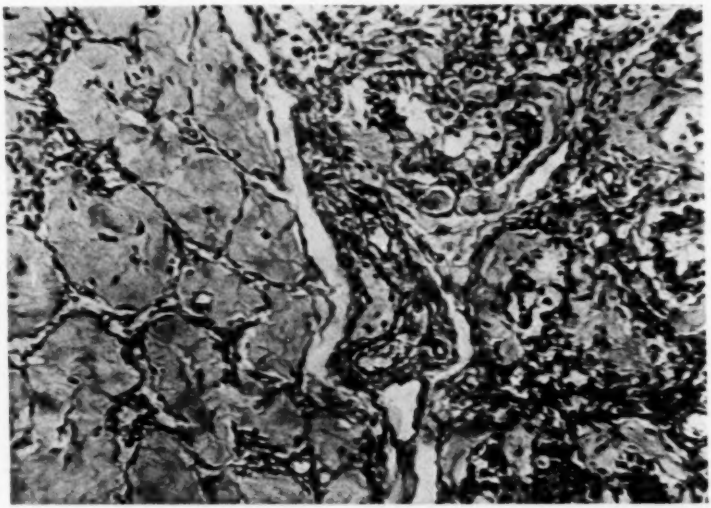

Fig. 3.—Atrophy of the testis, with hyalinization of the ducts and increase in interstitial tissue.

the peripheral position of the Nissl substance and the tigroid marking were distinct. This nucleus passed gradually over into the nucleus perifornicalis, lying around the fornix. The cells were large, dark and round or oval, sometimes even polygonal. The tigroid substance was rather diffusely scattered, the nucleus lying centrally, with good, clear spurs. No pathological features were observed in the cells of these nuclei. Lateral to the tuber cinereum were the nuclei tuberis—a medial (fig. 8) and a lateral. Both were very distinct, with their cells with light-colored protoplasm with slender spurs (fig. 9).

The transition from the pars tuberalis to the pars mamillaris was characterized by the large cells of the nucleus hypothalamicus posterior. The nucleus mamillaris medialis and nucleus mamillaris lateralis and the nucleus intercalatus were normally developed, and the cells showed no particular abnormality. The nucleus hypothalamicus lateralis consisted of large, dark-colored cells, which superficially resembled the cells of the nucleus supraopticus and was well developed in this region.

Nucleus pallidoinfundibularis: This nucleus was seen in the vertical anteroposterior section between the lowest portion of the columna fornicis and the nucleus supraopticus. Together with the nucleus mammilloinfundibularis, the nucleus pallidoinfundibularis formed the nucleus hypothalamicus lateralis of Clarke, which stretched like a long band above the nuclei tuberes.

Comment.—This picture has been erroneously described by various authors as cell degeneration. The closely packed cells, their distinct spurs and the absence of neurophagia and cell shadows form a strong argument against the theory of degeneration of this nucleus. Also, here and there a few cell shadows could be detected; these were too few as compared with the numerous normal cells to be called typical nuclear degeneration. The nucleus lateralis thalami, together with the nucleus rostralis thalami and the nucleus medialis thalami, was normal in the Nissl preparations. The substantia nigra was well developed and conformed entirely with the classic description (Jakob [5]).

Nucleus ruber: The large ganglion cells type I, as well as the smaller ganglion cells with their very large nuclei, were to be seen. Sections of the lowest part of the brain stem were begun at the decussation of the pyramids.

Cranial nerve nuclei: The ventral nucleus of the nervous accessorius contained only a few cells; these were small and dark, pyknotic and often without visible spurs; they were not angular

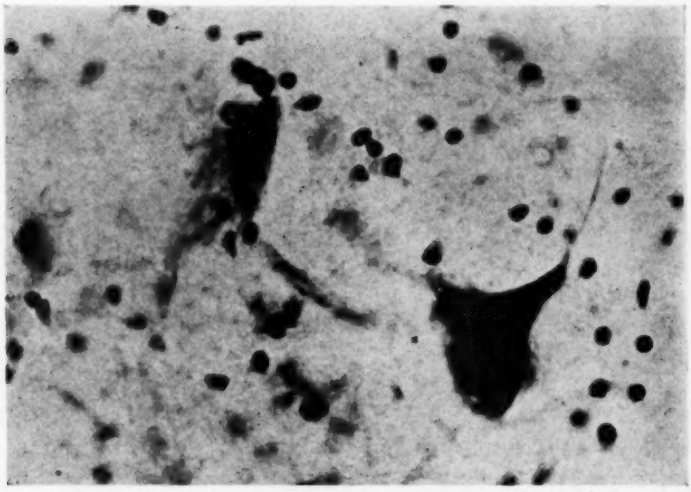

Fig. 4.—Degenerated and pyknotic motor cells in the anterior horn of the cervical portion of the cord.

or polygonal, but rounded. The nuclei were eccentric or invisible. The cells of the hypoglossus nerve showed the same sclerotic, pyknotic structure and cell degeneration as did the motor cells of the anterior horn in the spinal cord. The abducens nucleus was well developed on both sides. The nucleus of the seventh nerve had practically disappeared. This nuclear region was the only one in the central nervous system where a few glial nests were found. The left optic nerve was thinner and demyelinated (as a result of the enucleation of the left eye). There was a moderate falling out of Purkinje cells in the neocerebellum. No further abnormalities were noted. Specimens, stained according to the methods of Nissl and Weigert-Pal, of the nucleus caudatus, globus pallidus, putamen, nucleus dentatus, gyrus centralis anterior, gyrus frontalis superior, gyrus centralis posterior, gyrus parietalis inferior, gyrus temporalis medius and occipital pole were all normal.

REVIEW OF LITERATURE

I have previously reviewed the literature.[1] A summary will be given here, including one later publication. In all, 14 cases have been studied, five of which

5. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923.

were complicated by other neurological diseases; in 12 cases the central nervous system, and in 8 cases the endocrine glands, were examined histologically.

Steinert [6] (1909) described the first case, which was complicated by tabetic degeneration of the columns of Goll and Burdach. Steinert considered this degeneration to be of importance in the clinical picture. No such changes were found in any of the cases studied later. He described the typical degeneration in the muscles.

Hoffmann [7] (1919) in two cases observed no abnormalities in the central nervous system at autopsy. He observed the typical muscular degeneration and stated that there was nothing left of the roots but what he called *Trümmerfeld* (advanced degeneration of the motor roots, following advanced muscular degeneration).

Fischer [8] (1920) found no abnormalities in the central nervous system. Only the muscles showed pathological changes.

Fig. 5.—Normal sciatic nerve. Bielschowsky stain.

Hitzenberger [9] (1920) first described the histology of the testicular atrophy. He observed no agglomerations of tigroid substance in the nucleus of the seventh nerve but noted chromolysis and cell shrinkage. The nuclei were peripheral. The author found cellular changes throughout the spinal cord and peripheral nuclei without tigroid substance; and in general the cells of the anterior horn were few and shrunken.

6. Steinert, H.: Myopathologische Beiträge, Deutsche Ztschr. Nervenh. **37**:58, 1909.

7. Hoffmann, J.: Vergaderingsbericht, München, med. Wchnschr. **66**:519, 1919.

8. Fischer, L.: Klinische, psychopathologische und anatomische Beiträge zur Dystrophia myotonica, Ztschr. ges. Neurol. u. Psychiat. **58**:254, 1920.

9. Hitzenberger, R.: Über myotonische Dystrophie, Monatsschr. Psychiat. u. Neurol. **47**:249, 1920.

Bramwell [10] (1922), in connection with the clinical description of a case of his own, presented the examination of the central nervous system by James Dawson, who observed only striking pigmentation of the cells of the anterior horn and of the spinal ganglia.

Adie and Greenfield [11] (1923) did not find any anomalies in the central nervous system. The hypophysis exhibited many colloid particles in the acini. The adrenal glands revealed an irregular distribution of the lipids in the cortical layer. The authors considered these abnormalities, "although not absolutely pathological, certainly beyond what is normal." The peripheral nerves (ischiad, medians and musculospiralis), stained by the Weigert-Pal and the hematoxylin-Van Gieson methods, were also normal. They described the typical muscular degeneration.

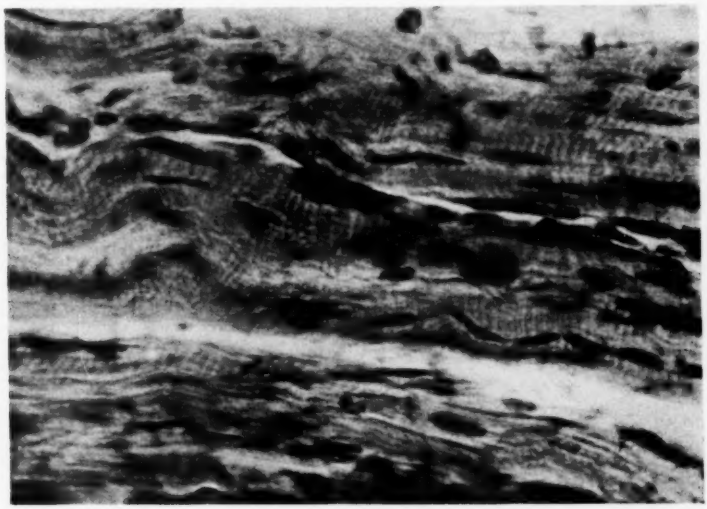

Fig. 6.—Trunk muscle. The nuclei lay in rows.

In a case of Weil and Keschner's [12] (1927) which is particularly well described and beautifully illustrated, it is regrettable that there were basal tuberculous meningitis and a spongioblastoma multiforme which occupied nearly the entire left temporal lobe. Microscopic examination revealed numerous abnormalities. The authors, however, considered that the changes around the third ventricle, pons and medulla oblongata might be caused by the meningitis and the tumor, although they would not ascribe to these agents the changes which they observed in the thoracic portion of the cord. The tuber cinereum, supraoptic nuclei and lateral and medial nuclei of the tuber presented pictures ranging from slight swelling to complete destruction of

10. Bramwell, E.: Case of Myotonia Atrophica with Autopsy, Proc. Roy. Soc. Med. **16**(Sec. Neurol.):11, 1923.

11. Adie, W. J., and Greenfield, J. G.: Dystrophia Myotonica, Brain **46**:73, 1923.

12. Weil, A., and Keschner, M.: Ein Beitrag zur Klinik und Pathologie der Dystrophia myotonica, Ztschr. ges. Neurol. u. Psychiat. **108**:686, 1927.

the cells, with dissolution of the plasma. The ventral nucleus of the tuber cinereum had suffered more than the dorsal one. The same picture was seen in the nucleus perifornicalis. The substantia nigra and the locus caeruleus showed a coarser granulation of the pigment, which lay in small compact heaps. In the pons they found cell groups around the aqueduct, with swelling and destruction of the Nissl substance, while other nuclei in the neighborhood were normal. In the spinal cord, the anterior horn was normal. Lateral horn cells in the thoracic portion of the cord were completely degenerated. The hypophysis showed a pronounced increase in the follicles of the anterior lobe. The thyroid gland contained extremely large follicles. The testis showed atrophy of the small ducts, which were lined with but one cell layer. There was a great increase in the number of Leydig cells. The outline of the

Fig. 7.—Calf muscle. The nuclei are gathered in closely packed nests.

adrenal cortex was blurred and irregular. Muscle abnormalities were similar to those described by other authors.

In the case described by Guillain, Bertrand and Rouquès [13] (1932), the center of the tuber cinereum and the infundibulum were intact. The central gray matter could not be examined because of the lacunar state of the organ. The case was atypical in that there was no familial history, no cataract, no testicular atrophy and no typical microscopic changes in the muscles. Remarkably enough, they discovered an adenoma the size of a nut in the cortex of one adrenal gland. The hypophysis was normal, except for small colloid cysts in the pars intermedia. The lateral horns of the spinal cord were intact. The authors noted atrophy of the motor cells of the anterior horns, and in the Bielschowsky preparations an irregular network was present in these horns throughout the entire spinal cord. A similar state was also

13. Guillain, G.; Bertrand, I., and Roquès, L.: Les lésions de la myotonie atrophique, Ann. de méd. **31**:180 (Jan.) 1932; Étude neurologique, series 6, p. 386, 1936.

seen in the third cranial nerve. It was strange that the neurofibrils in the axons and dendrites were normal. The authors considered these changes secondary results of the muscle degeneration.

The case of Keschner and Davison[14] (1933) is also minutely described and illustrated. It was only slightly complicated by a spongioblastoma of the corpus callosum, the size of a pea, protruding into the right ventricle. There were no clinical symptoms, and the tumor was small enough to be of negligible importance.

The authors observed degeneration of the nucleus paraventricularis and of some of the cells of the nucleus supraopticus. The nuclei tuberes were intact, as was the nucleus niger (this being in contrast to the cases of Weil and Keschner and of Sinnige and den Hartog). The thalamic nuclei were somewhat swollen;

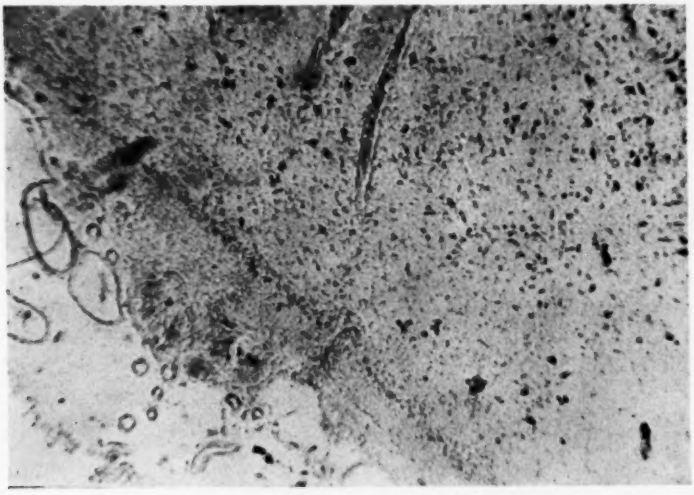

Fig. 8.—Medial nucleus of the tuber cinereum.

they were rich in pigment and had eccentric nuclei. The same picture was presented by the tuber cinereum. Likewise, slight changes were seen in the oculomotor nuclei. The locus caeruleus contained coarse pigment, and the dentate nucleus showed lacunas in the white matter. Furthermore, changes were observed in the cells of the anterior horn of the spinal cord and of the lateral horns. The anterior lobe of the hypophysis showed an increase in connective tissue and a decrease in the number of epithelial cells. The basophil cells were unusually large. In the middle the alveoli consisted almost entirely of eosinophils. In the frontal portion of the anterior lobe a considerable part was acellular and contained only connective tissue. The adrenal cortex revealed fibrosis, and portions of the fascicular and reticular layers were replaced by an avascular, edematous red substance. The testis exhibited complete aspermatogenesis and a larger number of Leydig cells than normal. The

14. Keschner, M., and Davison, C.: Dystrophia Myotonica, Clinicopathologic Study, Arch. Neurol. & Psychiat. **30**:1259 (Dec.) 1933.

authors consider it possible that the neural lesions were to be taken as retrograde degeneration. They doubted whether the "insignificant" changes hitherto described in the hypophysis and hypothalamic region could adequately explain the clinical manifestations.

Bielschowsky, Maas and Ostertag [15] (1933) observed pronounced pathological changes in the testis, adrenal glands and thyroid. The anterior lobe of the hypophysis was very small. The eosinophil cells appeared to have increased in number. There were notable changes in the nucleus basalis (ganglion of Meynert) and the adjacent dorsal portion of the nucleus supraopticus; furthermore, there was a falling out of cells in the lateral horn in the thoracic portion of the spinal cord. The peripheral nerves appeared normal with the Weigert-Pal stain, but showed pathological changes when impregnated with silver.

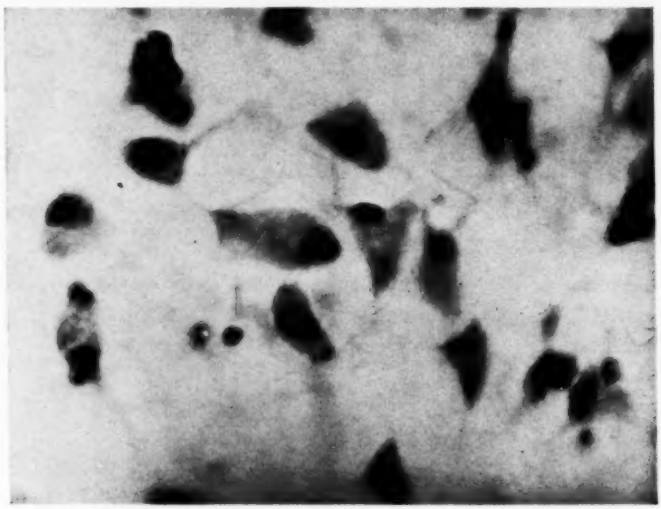

Fig. 9.—Medial nucleus of the tuber cinereum (oil immersion).

The article by d'Antona [16] (1941), which could be obtained only in a short summary, discussed merely the endocrine glands. The author found anomalies in the testis, adrenal glands, thyroid, thymus and, in one instance, the hypophysis.

The case described by Sinnige and B. J. C. den Hartog [17] (1950) was complicated by poliomyelitis in childhood but was otherwise typical except that the malady was not familial; no cataract could be found.

15. Bielschowsky, M.; Maas, O., and Ostertag, B.: Über Dystrophia myotonica (Myotonie atrophique), Vol. Jubilaire Marinesco, pp. 71-89, 1933.

16. d'Antona, L., cited, Zentralbl. ges. Neurol. u. Psychiat. **101**:137, 1942.

17. Sinnige, J. L. M., and den Hartog, B. J. C.: A Case of Dystrophia Myotonica Developing 15 Years After Poliomyelitis, Folia psychiat. neurol. et neurochir. neerl. (Brouwer Memorial Volume), p. 421, 1950.

Microscopical examination of the central nervous system revealed the following widespread lesions: atrophy, degeneration, necrosis, complete disappearance of ganglion cells; widespread reactive increase of micro-glia; neuronophagy; many fatty granule cells and pigment cells with a positive iron test in perivascular spaces and sometimes also in the leptomeninx; an excessive hyperaemia in some nuclei; some lymphocytic infiltrations in perivascular spaces and leptomeninx. These changes were notably present in those parts that are usually severely affected by poliomyelitis (gray matter of the spinal cord; spinal ganglia; formatio reticularis; nucleus vestibularis and other nuclei in the floor of the fourth ventricle; lateral portion of the substantia nigra; stratum griseum centrale of the aquaeduct; cerebellar cortex and dentate nucleus; nucleus paraventricularis). They were less marked where poliomyelitis manifests itself in a milder way (gyrus centralis anterior; oliva inferior; thalamus; nucleus ruber; globus pallidus). Important lesions were also found in the hypothalamus, histologically of the same nature; viz., in nuclei supra-optici; area prae-optica; nucleus prae-opticus, nucleus paraventricularis and to a lesser extent in nucleus ansae-peduncularis; tuber cinereum; corpus mammillare.

They found a glial *stick*, the central canal had completely disappeared and was replaced by gliosis and proliferation of the ependymal cells. They stated the belief that this glial *stick* was of a reactive nature, and not congenital.

The authors also noted changes in the axis-cylinders and fusiform thickening of the nerves, in accordance with Bielschowsky's observations. There were a persistent thymus, a very atrophic testis, atrophy of the epithelium of the thyroid and typical lesions in the muscles. The adrenal cortex had many small adenomas (as in the case of Guillain, Bertrand and Rouquès). The hypophysis, unfortunately, was mislaid after the autopsy.

COMMENT

To summarize the literature on this subject would be almost impossible. Most writers, except for the French authors Guillain, Bertrand and Rouquès, are in agreement regarding the pathology of muscles, but not with respect to the abnormalities of the endocrine glands and nervous system. The more recent researches contradict the earlier ones. Steinert, Hoffmann, Fischer, Bramwell, and Adie and Greenfield noted few, if any, abnormalities, and those which they did observe were too insignificant to explain the clinical syndrome. All authors are agreed regarding the testicular atrophy, but opinions on the anomalies of the other glands have been less well defined. Anomalies in the anterior horns, as well as in the lateral horns (sympathetic cells), have been described by Hitzenberger; Weil and Keschner; Keschner and Davison; Guillain, Bertrand and Rouquès, and Sinnige and den Hartog.

Anomalies in the hypothalamus and the so-called sympathetic regions around the third ventricle, aqueduct and fourth ventricle have been described, though briefly as a rule, by Weil and Keschner, Keschner and Davison, and Bielschowsky, Maas and Ostertag, as well as by Sinnige and den Hartog. In the case of Weil and Keschner, the conclusion reached regarding these regions was complicated by the presence of the large tumor in the temporal lobe and the basal meningitis. Keschner and Davison stated that it is difficult to decide whether any pathologic change exists in the nucleus paraventricularis and nucleus supraopticus even in a normal brain, and they are therefore doubtful regarding the significance of the lesion described in their case. Greving [18] stated that these nuclei always give the impression of being in a state of "*primäre Zellreizung*."

18. Greving, R., in Müller, L. R.: Lebensnerven und Lebenstriebe: Dritte wesentlich erweiterte Auflage des vegetativen Nervensystems, Berlin, Julius Springer, 1931, p. 115.

Other authors have described some interesting features in addition; for instance, Hitzenberger described an abnormality in the nucleus of the seventh nerve, and Guillain and associates, and Keschner and Davison, changes in the nucleus of the third nerve. Adie and Greenfield found the peripheral nerves intact. Bielschowsky, Maas and Ostertag observed anomalies of the peripheral nerves only with silver impregnation. Sinnige and den Hartog saw fragments of the axis-cylinders, corkscrew-like spirals and fusiform swellings.

In my case, the medial nucleus of the tuber cinereum (which, according to Bustamanta, is the sexual nucleus in the rabbit and, according to Spatz, Diepen and Gaupp,[19] is the sexual nucleus also in man) was intact. In view of the severe atrophy of the testis and the changes in the anterior lobe of the hypophysis which were described before, it is suggested that the main lesion must exist in the hypophysial portion of the hypophysiohypothalamic system! It is very likely that the gross atrophy of the testis was the result of this lesion. It is suggested that the other symptoms of dystrophia myotonica (myotonia, muscular atrophy and cataract) are equally the result of this lesion.

SUMMARY

The case described is characterized by the following features: (1) increase in the basophil cells and decrease of the eosinophil cells of the hypophysis (counted by the method of Rasmussen); (2) atrophy of the testis; (3) typical anomalies in the muscles; (4) normal hypothalamic nuclei, and (5) moderate secondary retrograde changes (pyknosis, shrinking and falling out) in the motor ganglion cells of the anterior horns in the cervical and thoracic portions of the cord (the rest of the cord was not available) and, especially, in the facial nucleus.

CONCLUSION

Dystrophia myotonica is a hereditary disease giving rise to cataract and abnormalities in the muscles and the endocrine glands. It is suggested that the pronounced abnormality of the hypophysis is the primary cause of the pathological changes.

Prof. Dr. A. Biemond supervised the preparation of the sections; Dr. D. B. Kroon and Mr. J. H. C. Ruyter stained the sections of the hypophysis; Dr. J. C. van Andel gave permission for the autopsy, and Mr. P. J. J. Verheusele gave technical assistance.

19. Spatz, H.; Diepen, R., and Gaupp, V.: Zur Anatomie des Infundibulum und des Tuber cinereum beim Kaninchen, Deutsche Ztschr. Nervenh. **159**:229, 1948.

LESIONS OF TRANSORBITAL LOBOTOMY

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TRANSORBITAL lobotomy is a rather new procedure, and a relatively safe one, so that up to the present time there has been little material for the study of the lesions produced by the operation. Preliminary reports by Freeman,[1] Freeman and Watts,[2] and Walsh [3] have been concerned principally with the location of the incisions in relation to the thalamofrontal radiation. The present study is based on 15 specimens from patients on whom necropsy was performed at various periods up to a year after operation. Details concerning these cases are given in the accompanying table.

In the peformance of transorbital lobotomy, a sharp slender instrument is inserted into the conjunctival sac 3 cm. from the midline, aimed parallel with the bony ridge of the nose and driven through the orbital plate to a final depth of 5 cm. within the frontal lobe. Lateral and medial cuts, through the white matter of the frontal lobe are made in this plane, and then, in most instances, the handle is deviated outward from the parasagittal plane between 20 and 30 degrees and strongly elevated in order to achieve the deep frontal cut. The extent of this incision varies, as indicated in profile photographs taken at the time of operation, being chiefly dependent upon the thickness and toughness of the orbital plate. In many operations the orbital plate fractures with an audible snap when the handle is pulled upon strongly enough. There is a resulting communication between the cranial cavity and the orbital tissues, which becomes filled with cerebrospinal fluid and blood, giving rise to swelling and ecchymosis of the lids, sometimes to the point of closure for a day or two. As the swelling subsides, the pigmentation changes from purplish through various shades to yellow and disappears in about two weeks. Subconjunctival hemorrhage is not infrequently observed.

Of the 15 patients on whom necropsy was performed, two died as the result of operative hemorrhage within a day or two, and one on the 19th day, after operative hemorrhage, as a result of pulmonary embolism. The bleeding point was on the medial aspect of the hemisphere in the first two cases and at the base in the last one. The hemorrhages were massive, producing great enlargement of the frontal pole and tending to dissect the ependyma away from

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From the Department of Neurology and Neurological Surgery, George Washington University School of Medicine.

Read by title at the Seventy-Sixth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 20, 1951.

1. Freeman, W.: Transorbital Lobotomy: The Deep Frontal Cut, Proc. Roy. Soc. Med. (Supp.) **42**:8-12, 1949.

2. Freeman, W., and Watts, J. W.: Psychosurgery, Ed. 2, Springfield, Charles C Thomas, Publisher, 1950.

3. Walsh, J.: Transorbital Leucotomy: Some Results and Observations, Lancet **2**:465, 1949.

the basal ganglia, with infiltration into the head of the caudate nucleus and as far down as the hypothalamus (Fig. 1). Four patients were in the terminal stage of carcinoma and died shortly after operation, one of them (Fig. 2) of suffocation due to a large carcinoma of the tongue. Six patients died within a few weeks or months of malignant disease. The problem of the relief of pain in these 10 patients with advanced malignant disease is discussed from the clinical standpoint by Williams and Freeman.[4] One patient sustained accidental burns during an epileptic attack (she had suffered from epilepsy for many years before operation for an involutional paranoid state), and one patient died in a paroxysm of asthma 11 months after

There was no case of rhinorrhea and no evidence of infection.

Data on Cases of Transorbital Lobotomy

Case No.	Sex and Age	Diagnosis	Post-operative Survival Period	Relief	Cause of Death	Anatomic Findings	Fig. No.
1	M 46	Carcinoma of tongue	1 hr.	?	Suffocation	Clean incisions in frontal white matter	2
2	F 26	Schizophrenia	8 hr.	?	Operative hemorrhage	Laceration, medial surface, clot	
3	F 23	Schizophrenia	20 hr.	?	Operative hemorrhage	Laceration, medial surface, clot	
4	F 65	Carcinoma of uterus	3 days	?	Carcinoma	Clean incisions entering ventricles	
5	F 39	Sarcoma of uterus	1 wk.	?	Convulsion	Clean incisions across thalamofrontal radiation	
6	F 74	Psychosis with cerebral thrombosis	19 days	?	Pulmonary embolism	Laminated hemorrhage, right frontal lobe	1
7	F 48	Carcinoma of colon	1 mo.	Good	Carcinoma	Clean incisions severing thalamofrontal radiation	
8	F 51	Carcinoma of breast	5 wk.	Good	Carcinoma	Collapsed hemorrhagic cavities in center of thalamofrontal radiation	6
9	F 39	Carcinoma of breast	2 mo.	None	Carcinoma	Sagittal (deep frontal) cuts lateral to thalamofrontal radiation	
10	F 65	Carcinoma of breast	10 wk.	Good	Carcinoma	Minute cortical lesions of rostral frontal cortex; no deep cut	
11	M 17	Carcinoma of colon	4 mo.	Poor	Carcinoma	Puncture wound (left); lateral cut (right); nicks in cortex	4
12	F 47	Carcinoma of colon	14 mo. 6 mo.	Poor	Carcinoma	First lobotomy Dec. 1948; second Aug. 1949; inadequate	
13	F 48	Paranoid state; epilepsy	9 mo.	Fair	Scald	Clean lesions beneath frontal poles; cortical scars (old) at upper end of Sylvian fissure	
14	F 55	Carcinoma of uterus	10 mo.	Good	Carcinoma	Clean lesions in thalamofrontal radiation	3
15	M 19	Schizophrenia; asthma	11 mo.	Good	Asthma	Clean lesion in thalamofrontal radiation (left); cyst (right)	5

PATHOLOGIC STUDY

Skull and Dura.—The perforations of the orbital plate were usually fairly symmetrically placed, about 3 cm. from the midline and 2 cm. behind the junction of the orbital plate with the frontal bone proper. In early cases there was protrusion of a small bit of orbital fat through the opening, but in later cases it was difficult to find the opening because of healing. A faint brownish stain of the underlying dura was seen in a few instances, and in one case there were a few delicate adhesions between the dura and the frontal lobe. In cases in which the deep frontal cut had been particularly extensive, the puncture opening was elongated, about 10 by 4 mm. In no case was there fragmentation of the orbital plate, nor was there any fracture line in the direction of the frontal sinus or optic nerve. There was no case of rhinorrhea and no evidence of infection.

4. Williams, J. M., and Freeman, W.: Transorbital Lobotomy for the Relief of Intractable Pain, A. M. A. Arch. Surg., to be published.

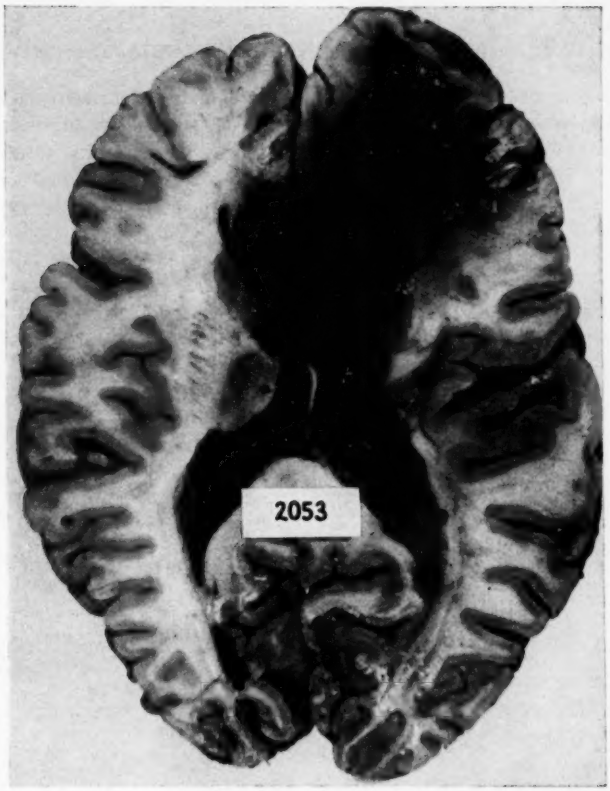

Fig. 1 (Case 6).—Postoperative hemorrhage into the right frontal lobe with large subcortical hematoma dissecting the basal ganglia and stripping the ependyma from these structures. An old cystic lesion, destroying the putamen and external capsule, is present on the right side. Death occurred on the 19th postoperative day, from pulmonary embolism.

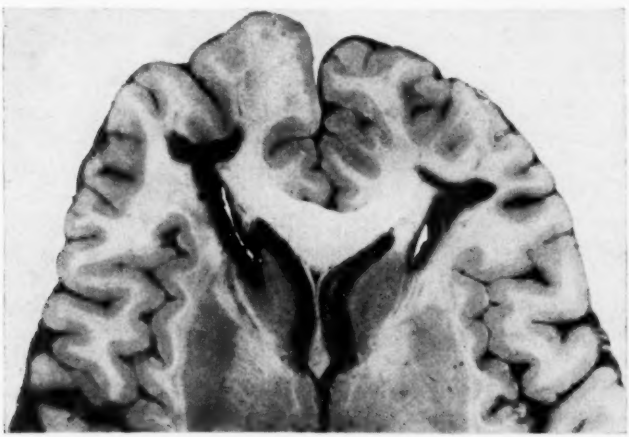

Fig. 2 (Case 1).—"Significant" incisions in the frontal white matter severing the thalamo-frontal pathway as it bends around the caudate nucleus and anterior horn of the lateral ventricle. Minor traumatism to the left caudate nucleus has occurred. Death occurred one hour after operation from suffocation due to carcinoma of the tongue.

Cortex.—The lesions of the cortex varied from a minute puncture wound, sometimes found with difficulty because of its location in the depths of a fissure, to a small area of laceration corresponding to the lesion of the orbital plate and dura (Fig. 3). The cortex along the line of the puncture showed destruction of a small area, ranging from 1 to 6 mm., affecting all layers and usually accompanied with some brownish or orange discoloration due to hemorrhage. Histologically, the track of the instrument was indicated by a fine core of connective tissue surrounded by slight gliosis, with a variable number of phagocytic microgliocytes. Myelin sheaths were degenerated only to a short distance beyond the actual wound, and there was no inflammatory infiltration. In certain cases the point or shaft of the instrument had penetrated the white matter of the frontal lobe and had lacerated the cortex on the superior or lateral surface of the frontal lobe (Fig. 4). Here the lesion was of different type, being usually a triangular or funnel-shaped

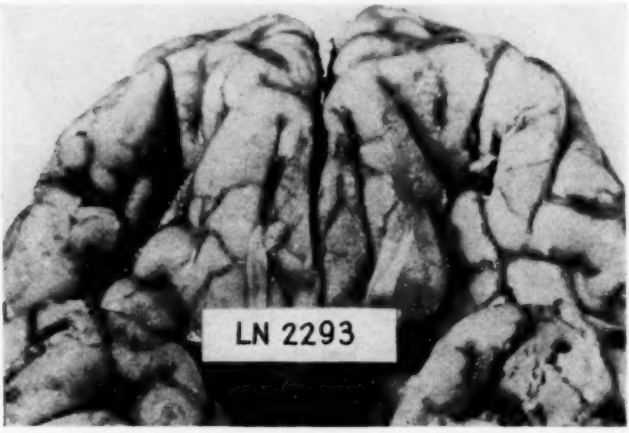

Fig. 3 (Case 13).—Lesions at the base of the frontal lobe which are larger than usual. This is the only instance in which adhesions had developed between the cerebral tissue and the dura. Operation afforded excellent relief from severe pain; survival period was 10 mo.

lesion, with the apex beneath the pia. The cortex in such lesions was cystic, with a delicate reticulum of connective tissue and scattered macrophages, with a little inflammatory reaction and some gliosis, and with more pronounced degeneration of the subcortical myelin sheaths. This type of lesion evidently resulted from laceration of an arterial twig in the depth of a fissure.

Subcortical White Matter.—The significant lesions of transorbital lobotomy were found in the subcortical white matter. These lesions may be considered from the standpoint of the pathologic changes and, more significantly, from the standpoint of their anatomic location. The lesion was sometimes an elongated slit in the white matter, whose sides came in contact with one another; it was bridged by delicate fibrous connective tissue and less gliosis than was found in the cortex. At other times the lesion consisted of an oval cavity with a more definite connective tissue lining, containing large numbers of gitter cells filled with pigment. Figure 5

shows dissimilar lesions on the two sides. The cavity evidently resulted from a small hemorrhage at the time of operation, although in this case there was no clinical evidence of hemorrhage.

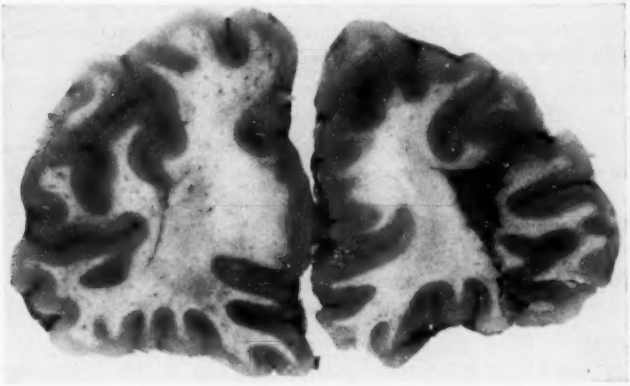

Fig. 4 (Case 11).—Complete failure of transorbital lobotomy to relieve pain of malignant disease. On the left side a simple puncture wound is visible, while on the right side the triangular lesion lies outside the thalamofrontal radiation, which can be vaguely appreciated as a slightly darker, crescentic tract in the central portion of the frontal white matter. This photograph shows involvement of the cortex at the point of entrance below and at the base of one of the fissures beneath the convexity on the right side. Survival period was four months.

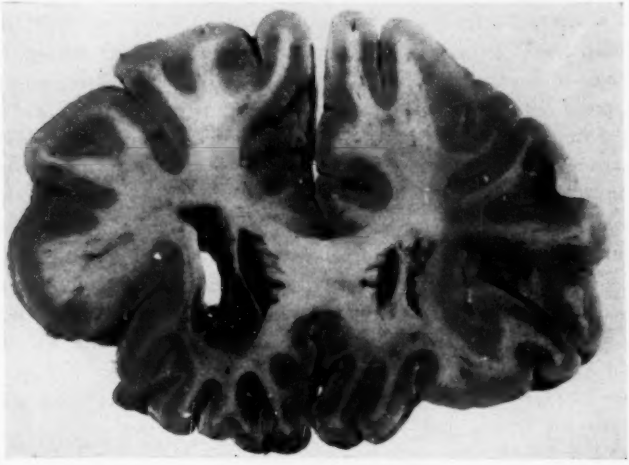

Fig. 5 (Case 15).—Frontal section through the genu of the corpus callosum. On the right side is a simple incision involving the thalamofrontal radiation as it passes between the anterior horn of the lateral ventricle and the anterior tip of the insula. On the left side the cavity reveals the remains of a hemorrhagic cyst in a similar location. Survival period was 11 mo.

The myelin sheaths lying anterior to the incision showed degeneration of the thalamofrontal radiation, resembling closely that described in cases of prefrontal

lobotomy.[5] The course of the degenerated fibers could be followed only a little way into the tip of the frontal pole, but there was some pallor of the region of the gyrus rectus on the side of the major lesion. There was also mild degeneration of the frontopontile tract, revealed better by proliferation of oligodendroglia than by pallor in myelin sheath preparations, and ending in the dorsomedial aspect of the rostral end of the pons.

The location of the subcortical incisions varied. In one case (failure of operation for the relief of pain) there was revealed on section a simple stab wound on one side, while on the other side there was a triangular lesion in the white matter with its apex at the point of entrance of the leukotome (Fig. 4). This lesion was about 5 cm. long and 1 cm. across at its upper margin. Both these incisions lay outside the thalamofrontal radiation. In two other cases (also operative failures) the deep frontal cut was not employed, and the lesions on either side were scarcely more than puncture wounds involving the cortex as much as the white matter at the tips of the frontal lobes. All these cases were early in the series.

Significant lesions in the frontal white matter severed the thalamofrontal pathways where these were concentrated between the head of the caudate nucleus and the cortex of the insula at its anterior extremity. Here the fibers running forward in the anterior limb of the internal capsule bend around the anterior horn of the lateral ventricle, forming an elbow, before spreading out in brush fashion to distribute themselves throughout the frontal white matter. Seen a little farther anteriorly (Fig. 6), these incisions lie just lateral to the commissural fibers of the genu of the corpus callosum. Since the incisions of transorbital lobotomy are somewhat oblique, they tend to cut across the elbow of the thalamofrontal projection.

The deep frontal cut severs most of the fibers in the thalamofrontal radiation, because some of these fibers, after passing in a compact band through the internal capsule, spread out in a ventral direction to engage the gyrus rectus and the basal part of the frontal lobe more laterally. The incisions of transorbital lobotomy at the base are less extensive than those found in prefrontal lobotomy. They seldom trespass upon the fibers underlying the lateral surface of the frontal lobe.

Caudate Nucleus and Ependyma.—The incisions of transorbital lobotomy sometimes injure the caudate nucleus and penetrate into the anterior horn of the lateral ventricle. This has been observed in only two instances, in both of which necropsy was carried out within three days of operation, so that the long-term results are unknown. Except for slight hemorrhage into the gray matter and definite laceration of the ependyma, there seemed to be no peculiar lesions. The question of penetration into the ventricles is of interest, particularly to the clinician. It probably happens fairly often, just as it does in prefrontal lobotomy (Watts-Freeman technique) but does not have any known clinical consequences. Indeed, it would seem safer to have a ready-made opening into the ventricle where blood could escape than to have blood accumulate in an intracerebral hematoma, with possibly

5. Freeman, W.: Die thalamo-frontalen Verbindungen in Licht der präfrontalen Lobotomie, Arch. Psychiat. **185**:624, 1950.

serious compression. This question cannot be answered on the basis of the present material.

Thalamus.—Retrograde degeneration in the thalamus was less extensive than that seen after most operations of prefrontal lobotomy.[6] The lesions were clearly evident, however, as manifested by loss of thalamic neurons, reduction in size of the nucleus medialis dorsalis, and proliferation of the oligodendroglia. They occurred mostly in the central portion of the nucleus, sparing the medial, or magnocellular, portion, as well as the lateral and ventral portions. Most of the cell loss was in the anterior portion of the medial nucleus. This conclusion, however, rests on only three cases in which serial sections of the thalamus were investigated after effective cuts had been made. In two others, in which the thalamofrontal radiation was untouched, serial sections showed no alteration in the medial nucleus or anywhere else within the thalamus.

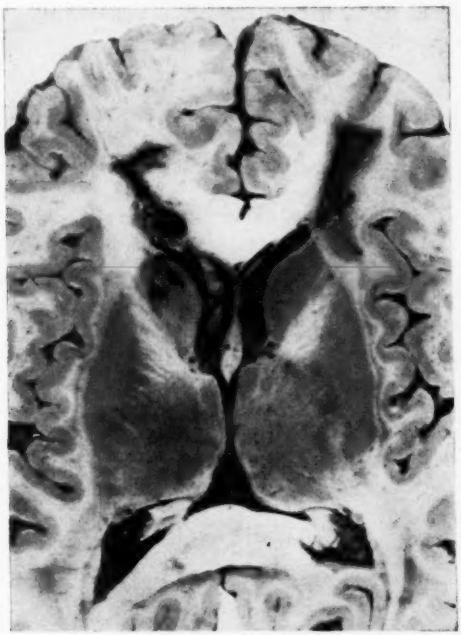

Fig. 6 (Case 8).—Horizontal section showing subcortical lesions of transorbital lobotomy. The cavities are filled with grumous material from partly absorbed hemorrhage. The thalamic radiation to the frontal poles is interrupted on both sides. Survival period was five weeks.

6. Freeman, W., and Watts, J. W.: Retrograde Degeneration of the Thalamus Following Prefrontal Lobotomy, J. Comp. Neurol. **86**:65-93, 1947. McLardy, T.: Thalamic Projection to Frontal Cortex in Man, J. Neurol., Neurosurg. & Psychiat. **13**:198-202, 1950. Yakovlev, P. I.; Hamlin, H., and Sweet, W. H.: Frontal Lobotomy: Neuroanatomical Observations, J. Neuropath. & Exper. Neurol. **9**:250-285, 1950.

SUMMARY AND CONCLUSIONS

Transorbital lobotomy produces minor lesions of the skull and dura. The cortex is usually traumatized very little. The distinctive lesions are within the white matter, the incision severing the thalamofrontal radiation just lateral to the anterior horn of the lateral ventricle, although sometimes penetrating the ventricle and lacerating the caudate nucleus. There is sometimes a hemorrhagic cavity in the frontal white matter, which evolves into a cyst with pigmented walls. Wallerian degeneration can be traced into the frontal lobe and also through the internal capsule into the pons. Retrograde degeneration on the thalamus is milder than that seen after prefrontal lobotomy.

From the pathologic standpoint, transorbital lobotomy is a clean-cut, selective operation for severing the thalamofrontal radiation.

PNEUMOENCEPHALOGRAPHIC STUDY OF CEREBROSPINAL-FLUID ABSORPTIVE-BLOCK MECHANISMS

A Study of the Mechanism Involved in Production of Increased Intracranial Pressure

ROBERT B. AIRD, M.D.
AND
DAVID ZEALEAR, M.D.
SAN FRANCISCO

DESPITE extensive research, the factors concerned with the dynamic equilibrium of cerebrospinal fluid are but imperfectly understood. Theories on the formation of cerebrospinal fluid consider the possibilities of dialysis, ultrafiltration,[1] or a secretory process, the last theory being supported by more recent data.[2] The site of formation of cerebrospinal fluid also remains in doubt. Earlier theories centered it in the choroid plexus,[3] while recent studies suggest that the cerebrospinal fluid is formed more diffusely in all perineuronal and perivascular spaces.[4] Physiological mechanisms influencing the formation of cerebrospinal fluid and abnormal factors capable of altering its formation remain even more obscure.

From the Divisions of Neurology and Neurological Surgery of the University of California Medical School.

1. Mestrezat, W.: Le liquide céphalo-raschidien, milieu intérieur de l'organisme, Rev. neurol. **1**:64-76 (Jan.) 1927. Fremont-Smith, F.: Nature of Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317-331 (March) 1927.

2. Flexner, L. B.: The Chemistry and Nature of Cerebrospinal Fluid, Physiol. Rev. **14**:161-187 (April) 1934.

3. Meek, W. J.: A Study of the Choroid Plexuses, J. Comp. Neurol. **17**:286-306 (May) 1907. Dandy, W. E.: Experimental Hydrocephalus, Tr. Am. S. A. **37**:397-428, 1919. Cushing, H.: The Third Circulation and Its Channels, Lancet **2**:851-857, 1925; Studies in Intracranial Physiology and Surgery: The Third Circulation, the Hypophysis, the Gliomas, The Cameron Prize Lectures, London, Oxford University Press, 1926. Howe, H. S.: Physiological Mechanism for the Maintenance of Intracranial Pressure, in The Intracranial Pressure in Health and Disease, Baltimore, Williams & Wilkins Company, 1929, p. 7. Schaltenbrand, G., and Putnam, T. J.: Untersuchungen zum Kreislauf des Liquor cerebrospinalis mit Hilfe intravenöser Fluoresceinspritzungen, Deutsche Ztschr. Nervenh. **96**:123, 1927.

4. Walter, F. K.: Wo ensteht der Liquor cerebrospinalis? Deutsche Ztschr. Nervenh. **90**:161-171 (Feb.) 1926. Kubie, L. W., and Retan, G. M.: Forced Drainage of the Cerebrospinal Fluid, J. A. M. A. **101**:354-358 (July 29) 1933. Wallace, G. B., and Brodie, B. B.: On the Source of the Cerebrospinal Fluid: Distribution of Bromide and Iodide Throughout the Central Nervous System, J. Pharmacol. & Exper. Therap. **70**:418-427 (Dec.) 1940. Weed, L. H., and Hughson, W.: Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by Intravenous Injections of Solutions of Various Concentrations, Am. J. Physiol. **58**:101, 1921. Foley, F. E. B.: Alterations in the Currents and Absorption of Cerebrospinal Fluid Following Salt Administration, Arch. Surg. **6**:587-604 (March) 1923. Mott, F. W.: The Oliver Sharpey Lectures on the Cerebro-Spinal Fluid, Lancet **2**:1-8 and 79, 1910. Jacobi, W.: Gefäss und Liquorstudien am Hirn des lebenden Hundes, Arch. Psychiat. **73**:126-138, 1925.

Although the anatomical pathways of cerebrospinal-fluid circulation are known,[5] a thorough investigation of the pathological conditions which may block these channels and of the resultant effects of such a block mechanism has not been made. Likewise, the absorptive bed and physiological factors concerned with absorption of the cerebrospinal fluid require clarification. Although the importance of the function of the arachnoidal villi [5b] in absorption is well known, a more diffuse subarachnoid absorption, not necessarily limited to the areas of the venous sinuses, has in addition been postulated.[6] The accessory role of other factors, such as the perivascular spaces,[7] venous pressure,[8] and osmotic pressure,[9] must also be considered.

It is clear, however, that an understanding of the dynamics of the cerebrospinal fluid requires a consideration of all these points, that is, its formation, circulation, and absorption. Physiological and pathological processes cannot alter one aspect of this dynamic equilibrium without influencing the others.

In the course of reviewing a large series of pneumoencephalograms, we have noted the frequent occurrence of a delayed absorption of the gases used for encephalographic injection (particularly ethylene and other rapidly absorbed gases) in patients who showed dilatation of the ventricular system and diminished or no subarachnoid filling. We have come to consider this triad of findings a roentgenological entity indicative of an absorptive block. This aspect of our pneumoencephalographic data has served to clarify our thinking with respect to some of the factors concerned with the equilibrium of cerebrospinal fluid and, for this reason, appears to us worthy of report.

MATERIAL AND METHODS

Satisfactory pneumoencephalograms were obtained under standardized conditions [10] on 1,272 patients. Adequate clinical studies were obtained in all cases in the University of California

5. (*a*) Weed, L. H.: Studies on Cerebrospinal Fluid, J. M. Research, **26**:21-118, 1914. (*b*) Locke, C. E., Jr., and Naffziger, H. C.: The Cerebral Subarachnoid System, Arch. Neurol. & Psychiat. **12**:411-418 (Oct.) 1924. (*c*) Iwanow, G., and Romodanewsky, K.: Über den anatomischen Zusammenhang der cerebralen und spinalen submeningealen Raume mit dem Lymphsystem; Methodik und wichtigste Beobachtungen, Ztschr. ges. exper. Med. **58**:596-607, 1927. (*d*) Key, E. A., and Retzius, G.: Studien in der Anatomie des Nervensystems und des Bindesgewebe, Stockholm, Samson & Wallin, 1876. (*e*) Clark, W. E.: On the Pacchionian Bodies, J. Anat. **55**:40-48, 1920-1921. (*f*) Wollard, H. H.: Vital Staining of the Leptomeninges, ibid. **58**:89-100, 1923-1924.

6. Dandy, W. E.: Where is Cerebrospinal Fluid Absorbed? J. A. M. A. **92**:2012-2014 (June 15) 1929. Scholtz, R. O., and Ralston, E. M.: Pathways of Absorption of Sodium Ferrocyanide from Subarachnoid Space into Venous System, Anat. Rec. **75**:365 (Nov. 25) 1939. Lindauer, M. A., and Griffith, J. Q., Jr.: Cerebrospinal Pressure Hydrocephalus and Blood Pressure in Cat Following Intracisternal Injection of Colloidal Kaolin, Proc. Soc. Exper. Biol. & Med. **39**:547-549, 1938.

7. Griffith, J. Q., Jr.; Fry, W. E., and McGuinness, A.: Experimental and Clinical Studies in Hydrocephalus, Am. J. Ophth. **23**:245-251 (March) 1940.

8. Myerson, A., and Loman, J.: Internal Jugular Venous Pressure in Man: Its Relationship to Cerebrospinal Fluid and Carotid Arterial Pressure, Arch. Neurol. & Psychiat. **27**:836-846 (April) 1932.

9. Weed, L. H.: Meninges and Cerebrospinal Fluid, J. Anat. **72**:181-215 (Jan.) 1938.

10. Aird, R. B.: Simplified Pneumoencephalographic Apparatus and Technique, J. Nerv. & Ment. Dis., to be published.

Hospital. The clinical classifications of the patients is shown in Table 1. Follow-up studies to determine the absorptive rate of the rapidly absorbed gases (ethylene and oxygen) used for pneumoencephalographic injection [11] proved adequate for 630 of these patients (Table 2).

The pneumoencephalographic interpretation was made without knowledge of the clinical findings to insure an objective evaluation of the material. A detailed examination of each portion of the ventricular and subarachnoid spaces was made in a predetermined and systematic way and recorded [12] on a punch card [13] under the following categories:

Ventricles

Size: Normal; slightly dilated; markedly dilated; unequally dilated

Shift: None; slight; marked; third ventricle shifted more or less than septum pellucidum; other

Distortion: None; depression; traction; other

Subarachnoid Spaces

Normal

Dilated: Slight, marked, general, focal

Obliterated: At vertex, convexities, base; focal, streaky, or other distorted form

TABLE 1.—*Classification of Patients Studied by Pneumoencephalography During the Years 1936-1946*

	Number of Patients
Convulsive states	
"Idiopathic"	422
Post-traumatic	147
Postinfectious	73
Brain-tumor suspects	309
Degenerative diseases of central nervous system (Mental retardation, demyelinating diseases, extrapyramidal diseases, etc.)	159
Psychiatric disorders	31
Cerebrovascular disorders (Hemorrhagic, embolic, thrombotic, arteriosclerotic)	33
Miscellaneous conditions (Headache of undetermined origin, diabetes insipidus, retrobulbar neuritis, etc.)	98
Total	1,272

The clinical findings, laboratory data, pathological observations, and diagnosis were recorded on the same card to facilitate an efficient cross correlation and integration of all the data.

Since the pneumoencephalographic technique used in this study has been described in detail in another paper,[14] it will suffice for the purpose of the present report merely to emphasize the essential principles.

1. Ethylene gas was used to replace the cerebrospinal fluid, since it was important to have a pure gas the solubility of which would insure a sufficiently constant and rapid rate of absorption or disappearance to make possible a comparative study under normal and abnormal conditions. A relatively rapid rate of absorption is important if variable physiological conditions, which might influence the rate of absorption over prolonged periods, are to be minimized. The factors essential for an adequate evaluation of the rate of disappearance of ethylene from the central nervous system have been enumerated and discussed in a previous paper.[11]

11. Aird, R. B.: The Absorption of Ethylene Gas Following Encephalography, with a Clinical Correlation in 164 Cases, Radiology **30**:320-336 (March) 1938.

12. Aird, R. B., and Bowditch, S. C.: Cortical Localization by Electroencephalography, J. Neurosurg. **3**:407-420 (Sept.) 1946.

13. E-Z Sort Systems, Ltd., 45 2d St., San Francisco.

14. Aird, R. B.: Encephalography with Anesthetic Gases, Arch. Surg. **34**:853-867 (May) 1937.

Oxygen was used in the cerebrospinal fluid-gas exchange in 45 of the 630 patients. Its slower absorptive rate, however, makes it less reliable than ethylene for the type of analysis required in this study. Consequently, the absorptive rate was considered normal in all patients in whom oxygen was used, except those showing a gross and obvious delay even for this more slowly absorbed gas. Curves showing the relative absorptive rates of ethylene, oxygen, and air are reproduced in Figure 1.

2. An exchange of cerebrospinal fluid and gas was effected in all instances as completely as possible, except that volume exchanges in excess of 200 cc. were not considered desirable or necessary. Maximal exchanges within the usual range are desirable with rapidly absorbed gases to insure an adequate pneumoencephalographic study. As Pendergrass [15] and others have emphasized, the principal source of error in the roentgenographic interpretation of pneumoencephalograms lies in an inadequate exchange and the consequent unsatisfactory visualization of the ventricles and subarachnoid spaces. Maximal exchanges within the 200 cc. limit mentioned have not been associated with alarming clinical reactions. In fact, evidence has been adduced [16]

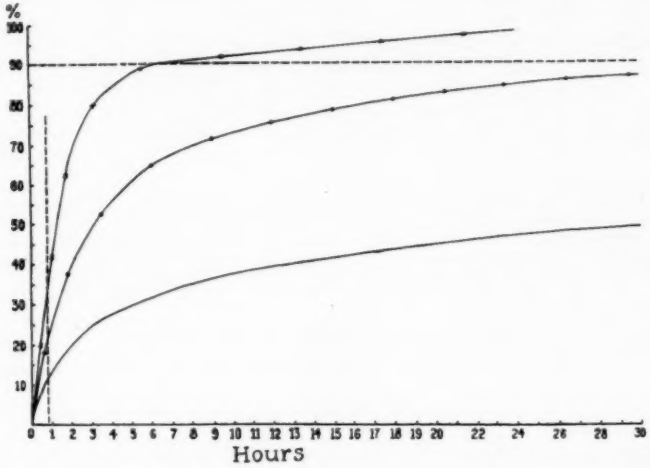

Fig. 1.—Curves representing the estimated lower limits for the "normal" rate of absorption of ethylene (line with crosses), oxygen (line with dots), and air (plain line) after their pneumoencephalographic injection. Time is indicated in hours on the abscissa, and the estimated percentage absorption of the gases, on the ordinate.

which suggests that the clinical reaction following pneumoencephalography is lessened in intensity and duration when rapidly absorbed gases, such as ethylene, are used.

3. General anesthesia was used to obviate the early reaction and to insure an efficient and satisfactory roentgenographic study. Although it is generally agreed now that pneumoencephalography, like any other operative procedure associated with pain and shock, warrants the use of an anesthetic, there is considerable divergence of opinion as to the choice of anesthetic agents. The basal anesthesia, tribromoethanol solution U. S. P. (avertin®), 90 to 100 mg. per kilogram of body weight, was used with adults in this study, since it has a prolonged action, which is desirable in a procedure associated with a prolonged reaction. Preliminary morphine and scopolamine and supplementary inhalation or intravenous injection of anesthetics were

15. Pendergrass, E. P.: The Value of and Indications for Encephalography and Ventriculography, with Discussion of the Technic, S. Clin. North America **10**:1461-1475 (Dec.) 1930.

16. Aird, R. B.: Experimental Encephalography with Anesthetic Gases, Arch. Surg. **32**:193-217 (Feb.) 1936.

employed as necessary to obtain satisfactory narcosis. Ether anesthesia proved satisfactory in children, since their reaction to pneumoencephalography is in general less severe and prolonged than in adults.

4. A simultaneous and continuous exchange of cerebrospinal fluid and gas was effected under constant pressure.[10] The initial pressure under the conditions of the procedure (anesthesia and a sitting position) was obtained and was maintained throughout the exchange.

5. The roentgenographic study included a single lateral view of the head taken with the patient in the sitting position and a series of right-angle projections (vertical and horizontal transverse) with the occiput, brow and right and left sides of the head, in turn, against the cassette, and with the patient in a recumbent position. This phase of the technique has been described in detail [17] and follows the principle used by Lysholm [18] and others. In addition, stereoscopic projections were obtained in those positions in which it was felt that the lesion might best be visualized.

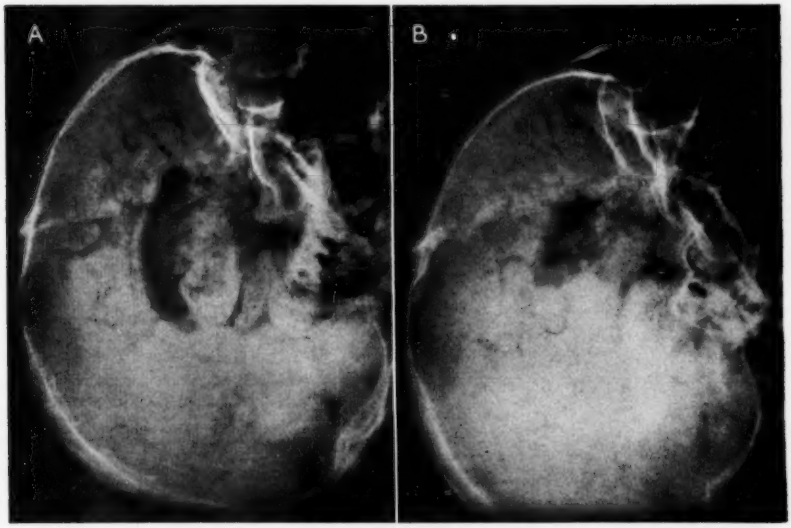

Fig. 2.—Original transverse horizontal projection with brow up (*A*) and the three-hour follow-up projection in the same position (*B*). E. H., a man aged 35, had spells and blurred vision of two years' duration. The neurological findings were normal except for a bilateral Babinski sign. The diagnosis was convulsive state of secondary type.

A pneumoencephalographic study was performed, with exchange of 140 cc. of cerebrospinal fluid and ethylene gas. The roentgenographic diagnosis was slight increase in size of the lateral ventricles, complete absence of subarachnoid spaces at the vertex, and definite delay in absorption of gas, it being estimated that 50 to 60% was still present at the end of three hours.

Follow-up lateral projections were obtained after a three-hour interval, and occasionally at other intervals as well. This afforded the data essential for the determination of the rate of absorption in each case (Fig. 2). Independent estimations of the percentage of absorption, as

17. Stone, R. S., and Jones, O. W.: Encephalography: A Review of 103 Cases, and a Report of Postmortem Studies on the Injection of Air, Radiology **21**:411-419 (Nov.) 1933.

18. Lysholm, E.; Ebenius, B.; Lindblom, K., and Sahlstedt, H.: Das Ventrikulogramm; dritter und vierter Ventrikel, Acta radiol. Supp. 26, pp. 1-124, 1935. Ebenius, B., and Sahlstedt, H.: Röntgentechnik, ibid. Supp. 24, pp. 1-75 1935; Das Ventrikulogramm; die Seitenventrikel, ibid. Supp. 36, pp. 1-99, 1937.

well as repeated estimations made at different times on the same follow-up roentgenograms, showed that such estimations were consistent and reliable to within 10%. Correlation of all available clinical data with the absorption rates of ethylene resulted in the following groups:

Retention of Gas, %	
0-20	Normal
20-30	Borderline or slightly delayed absorption
30 or more	Moderately or greatly delayed absorption

TABLE 2.—*Correlation of Clinical Diagnosis with Absorptive Rate of Gases* in the Pneumoencephalographic Studies of 630 Patients*

No. of Patients	Clinical Classification Convulsive States	Normal Absorption (0-20% Remaining) No.	%	Borderline Absorption (20-30% Remaining) No.	%	Delayed Absorption (30% or More Remaining) No.	%
236	"Idiopathic"	199	84	13	6	24	10
95	Posttraumatic	59	61	12	13	24	26
50	Postinfectious †	22	44	7	14	21	42
32	Posttraumatic head syndrome	20	63	1	3	11	24
51	Brain-tumor suspects (by pneumographic diagnosis)	27	53	8	16	16	31
86	Degenerative diseases of central nervous system	51	60	14	16	21	24
22	Cerebrovascular disorders (subarachnoid, hemorrhage, emboli, etc.)	12	54	3	14	7	32
58	Miscellaneous conditions (headache, psychiatric disorders, etc.)	42	73	6	10	10	17
630	Total	432	..	64	..	134	..

* Only cases in which ethylene and oxygen were used are included. The absorptive rates were based on a three-hour follow-up roentgenogram, made in the case of ethylene, and a 24-hour follow-up roentgenogram, made in the case of oxygen.

† Meningitis and/or encephalitis.

TABLE 3.—*Correlation of Pneumoencephalographic Findings and the Absorptive Rates for Ethylene and Oxygen in 630 Patients*

Absorption, % of Gas Remaining at 3 Hr.	Group 1 Ventricles Normal Subarachnoid Spaces Normal No.	%	Group 2 Ventricles Normal Subarachnoid Spaces Dilated No.	%	Group 3 Ventricles Dilated Subarachnoid Spaces Normal No.	%	Group 4 Ventricles Dilated Subarachnoid Spaces Dilated No.	%	Group 5 Ventricles Normal Subarachnoid Spaces Decreased No.	%	Group 6 Ventricles Dilated Subarachnoid Spaces Decreased No.	%
Normal (0-20%) 432 patients	175	91	80	87	35	83	91	70	27	59	24	21
Borderline (20-30%) 64 patients	5	3	6	6	3	7	14	10	5	11	31	25
Delayed (30%+) 134 patients	12	6	6	7	4	10	29	20	14	30	69	54
Total 630	192	100	92	100	42	100	134	100	46	100	124	100

RESULTS

The rate of gas absorption in accordance with this threefold classification is given in Tables 2 and 3 for the 630 patients studied, Table 2 showing the clinical, and Table 3 the pneumoencephalographic, correlation. In addition, Figure 3 gives a graphic representation of the absorptive rates for the various pneumoencephalographic categories.

The findings indicate an interesting correlation between the clinical data and the absorptive rates. The absorptive rates were normal for the great majority of patients whose history was not suggestive of a pathological condition commonly associated with alterations of cerebrospinal-fluid dynamic equilibrium, such as

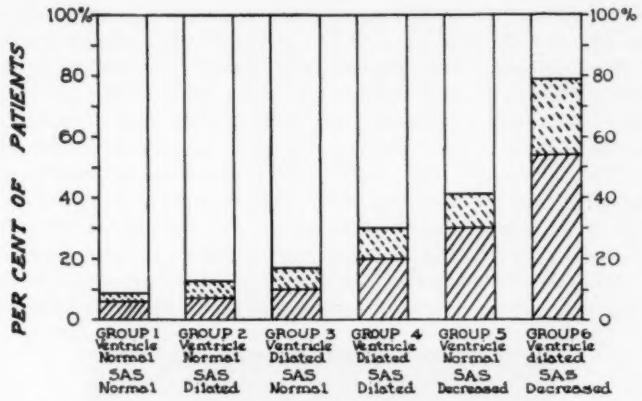

Fig. 3.—Correlation of pneumoencephalographic findings and the absorptive rates for ethylene and oxygen for 630 patients. Values for normal absorption (20%) are indicated by plain rectangles; values for borderline absorption (20 to 30%), by rectangles with partial cross hatching, and values for delayed absorption (30%+), by rectangles with complete cross hatching. *SAS* stands for subarachnoid spaces.

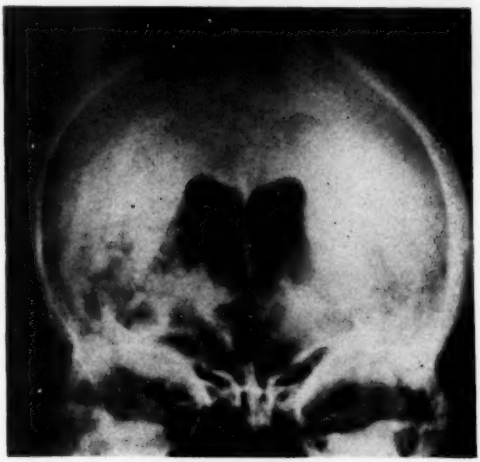

Fig. 4.—Anteroposterior projection with brow up.

L. B., a woman aged 26, had had spells since the age of 4 yr., when she had a very severe attack of "whooping cough." There had been progressive mental deterioration since the age of 14. Physical and neurological examinations showed an essentially normal condition except for obvious mental retardation. The diagnosis was convulsive state and mental retardation of probable postpertussis origin.

The pneumoencephalographic study was performed, with exchange of 150 cc. of cerebrospinal fluid and ethylene gas. The roentgenographic diagnosis was slight symmetrical dilatation of all ventricles; no supracortical subarchnoid filling, except to minimal degree in the low frontal and temporal areas, and delay in gas absorption, 35% being estimated to be still present after three hours.

infection, tumor, or trauma. For example, the absorptive rate was within normal limits for 84% of patients with convulsive states who had no history of infection or trauma. Similarly, in the miscellaneous group (headaches of undetermined origin, psychiatric conditions, etc.) the absorptive rate was generally normal. On the other hand, in patients with convulsive states secondary to meningitis or meningoencephalitis the absorptive rate was normal in only 44%. Brain tumors, cerebrovascular disorders (subarachnoid or other intracranial hemorrhages, emboli, thromboses), and degenerative disease also were manifested by delayed absorption in a high percentage of patients. A review of the group with degenerative diseases of the central nervous system, which consisted of 59 patients with "mental retardation" and 27 with other conditions (cortical atrophy, multiple sclerosis, etc.), indicated that 21 patients showed a definite or marked delay in absorption. Eighteen of these

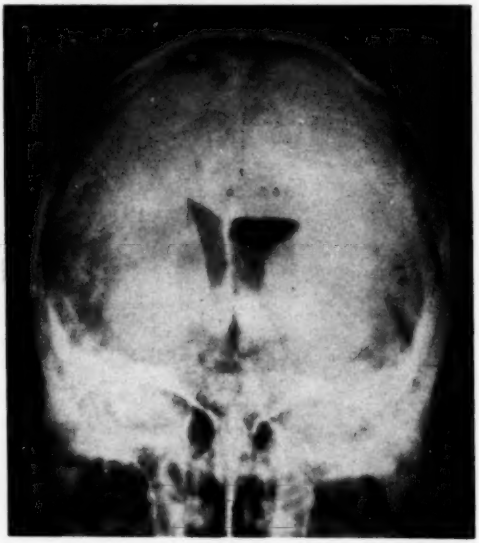

Fig. 5.—Anteroposterior projection with brow up.

E. R., a man aged 56, had had Jacksonian seizures involving the right leg and the right lower part of the abdomen in the previous 10 mo., with progressive course. Physical and neurological examinations revealed an essentially normal condition except for slight underaction of the right lower part of the face, increased patellar and Achilles reflexes on the right, and sustained ankle clonus on the same side. The diagnosis was tumor of the left frontal lobe.

A pneumoencephalographic study was performed, with exchange of 130 cc. of cerebrospinal fluid and ethylene gas. The roentgenographic diagnosis was dilatation of the left lateral ventricle with depressed roof; tilting of the septum pellucidum to the right; no filling of the subarachnoid spaces, except to a limited extent frontally, and delay in gas absorption, 35% being estimated to be still present after three hours. The diagnosis was parasagittal tumor of the left motor cortex.

Operation consisted in osteoplastic craniotomy in the left frontoparietal area and removal of a parasagittal meningioma of the angiomatous type.

belonged in the group with mental retardation, again suggesting a relation between a delayed rate of absorption and pathological processes of a meningoencephalitic character.

From a pneumoencephalographic standpoint, it appeared that delay in absorption corresponded closely with processes involving the cerebrospinal-fluid channels. Specifically, the roentgenographic findings in such cases were (1) small, streaky, or partially obliterated subarachnoid channels, and (2) "large normal," or definitely dilated, ventricles. Typical examples of this roentgenographic entity are shown in Figures 4 and 5, the first in a case of a convulsive state of meningoencephalitic origin, and the second, in a case of brain tumor.

COMMENT

Factors related to the circulation and absorption of the cerebrospinal fluid appear by far the most important in determining the dynamic equilibrium of the cerebrospinal fluid. These and other factors related to the formation of cerebrospinal fluid presumably have a considerable margin of safety under normal conditions. The extent of the absorptive bed and the size of the subarachnoid channels leading to it probably are adequate to cope with all ordinary and most abnormal fluctuations of cerebrospinal-fluid formation. On the other hand, if under the term absorptive mechanism we include the cerebrospinal-fluid circulation from the point of its formation to the absorptive bed, as well as the venous drainage of the cranium, pathological processes involving the absorptive mechanism account for the great bulk of conditions associated with abnormalities of cerebrospinal-fluid equilibrium. Since the venous drainage is only occasionally impaired, and in general may be ruled out by either a physical examination or cerebrospinal-fluid-pressure determinations with differential jugular compression, the most important cause of abnormal cerebrospinal-fluid dynamics is to be found in processes affecting the cerebrospinal-fluid circulation and its main absorptive bed in the supracortical subarachnoid spaces. This concept has been emphasized from another point of view by Bagley and his co-workers.[19]

As a result of such considerations, the importance of an adequate pneumoencephalographic study of the subarachnoid channels in conditions associated with abnormal cerebrospinal-fluid dynamics immediately becomes apparent. Since ventriculography fails to afford the desired information, pneumoencephalography is the diagnostic procedure of choice except in cases with evidence of increased intracranial pressure, in which it cannot be used with safety. Furthermore, in those patients in whom ventriculography has failed to show the cause of their increased intracranial pressure, it is our belief that a lumbar-subarachnoid gas injection may be done safely directly after the ventriculographic procedure if one ventricular needle is left in place. Although such a combined procedure is not frequently indicated, it has afforded critical information in difficult diagnostic problems when ventriculography alone failed to reveal the lesion or point of obstruction of the cerebrospinal-fluid circulation.

The association of meningoencephalitis and residual adhesive changes, large ventricles, and gliosis is well known. When the degree of gliosis differs in the two hemispheres, or predominates in one portion of one hemisphere, as indicated by an

19. Bagley, C., Jr.; Thompson, R. K. S., and Crosby, R. M. N.: Distention of the Subarachnoid Space with Cerebrospinal Fluid in Infants: Enlargement of the Head and Spasticity; Surgical Correction, Ann. Surg. **129**:662-76 (May) 1949.

asymmetry of the two lateral ventricles or a focal ventricular and subarachnoid dilatation, it is obvious that the patient has suffered from a severe encephalitic process. In many instances, however, the ventricles are symmetrically enlarged, and the subarachnoid spaces are uniformly dilated up to the point at which they are obstructed. One cannot be sure in such cases whether the ventricular dilatation is entirely secondary to subarachnoid obstruction, or whether it may be due to a diffuse meningoencephalitis which involves the entire brain about equally. Symmetrical ventricular dilatation secondary to deep degenerative changes in the white matter, with or without an associated meningoencephalitic process, diffusely involving both cerebral cortices, is conceivable. Although diffuse meningoencephalitis alone might produce such a picture, it is likely that a disturbance in the absorptive mechanism is involved in most instances. It should be added that these conditions are not necessarily mutually exclusive, and both may be present in varying degree in most cases. Even in the obvious cases of encephalitis with asymmetrical dilatation of the ventricular and subarachnoid spaces, the dilatation may have been produced in part by an obstructive process in the acute stage of the inflammatory condition. Certainly, such a possibility must be suspected in those patients showing a bilateral and generalized dilatation of the subarachnoid spaces up to the point of obstruction.

The pathological physiology responsible for the characteristic roentgenographic picture associated with a delay in the absorptive rate of the gas, and the explanation of the fact that these changes may coexist with a normal cerebrospinal-fluid pressure and compensated cerebrospinal-fluid circulation, have been discussed in an earlier paper.[11] They would appear to be best explained in terms of the difference in the physical state and ease of transfer of gases and liquids through channels of small caliber. Because of the viscosity and surface tension of fluids, a gas after its encephalographic injection displaces with difficulty the cerebrospinal fluid in the smaller channels of the supracortical subarachnoid spaces. This would be particularly likely to occur if these channels were partially blocked and further constricted, as, for example, by supracortical arachnoidal adhesions. Under such conditions, the gas would be limited for the most part to the larger channels. This would tend to exaggerate the appearance of the obstructive process.

The rate of disappearance of the gas is determined largely by its rate of solubility in the cerebrospinal fluid and the surface area of exposure or interface between the gas and the cerebrospinal fluid. The latter factor explains the relatively rapid disappearance of gas from the subarachnoid spaces, where it is broken up into bubbles or small collections, as opposed to the slower rate of disappearance from the ventricles, where there is a single interface, of minimal size, between the fluid and the gas. The relatively rapid absorption of gases in the subarachnoid spaces becomes even more marked when a highly soluble gas, such as ethylene, is used. This tends to result in an incomplete visualization of the smaller subarachnoid channels, and hence may also exaggerate the appearance of an "obstructive process," if present.

Restriction of the gas to the larger subarachnoid channels by a partial obstructive process not only "exaggerates the appearance of the obstructive process," but, by reducing the absorptive interface between gas and cerebrospinal fluid, actually delays the rate of absorption. As indicated by the results obtained in this study,

the retardation in the absorption of ethylene occurring under such conditions is appreciable and definitely antedates obstructive mechanisms of the cerebrospinal-fluid circulation associated with increased intracranial pressure. The absorption of gas thus serves as a delicate and early diagnostic test of partial obstructive processes.

Therefore, although a delay in the absorption of gas does not necessarily indicate a decompensation of the cerebrospinal-fluid circulation, it does suggest a limited margin of safety in the absorptive mechanism. At this stage the slow disappearance of the gas is consistent with ventricles of normal size and normal cerebrospinal-fluid pressure. If the process is progressive, as in the case of a chronic, low-grade leptomeningitis, this early change foreshadows the alterations to come with a progressive blocking of the absorptive bed or the channels leading to it, namely, a delayed absorption of cerebrospinal fluid, increased intracranial pressure, and hydrocephalus.

If such a process should regress at any stage, as after the acute stage of meningoencephalitis, the absorptive block might be relieved and the cerebrospinal-fluid circulation again become compensated. Only if the residual absorptive mechanism were still adequate for the absorption of all cerebrospinal fluid formed, however, would the cerebrospinal-fluid circulation be compensated and the pressure again become normal. Under such circumstances, the subarachnoid spaces presumably would not return to normal, and their partial obstruction or reduced size would still be associated with restricted filling on pneumographic study and a delayed rate of gas absorption. Whether or not dilated ventricular and basal cisterns would appear as residual structural changes in a pneumographic study after such an acute inflammatory process would depend on such factors as the duration and severity of the acute condition and the site of obstruction.

The fact that the typical roentgenographic picture associated with delayed absorption was found in 21 of 51 brain-tumor suspects (Table 2, Fig. 4) raises the question of whether or not this same obstructive mechanism may explain the disturbed cerebrospinal-fluid dynamics associated with space-consuming processes. Since the pneumoencephalographic procedure was not performed in the presence of any appreciable increase of intracranial pressure, it must be stressed that the patients of this group entered the hospital for study because of symptoms and signs referable to the local effects of their tumors rather than to increased intracranial pressure.

Another group of five tumor suspects was studied at a later stage of their disease, when there was definite evidence of increased intracranial pressure. A combined procedure was carried out, that is, a pneumoencephalographic following an indecisive ventriculographic study and showed in all a decrease in size or absence of the subarachnoid spaces and definite ventricular dilatation. This suggests that such a syndrome is a frequent accompaniment of tumors, particularly in the later stages, when a rise in intracranial pressure has become manifest. In further substantiation of this point, dilatation of at least one lateral ventricle was found in 90 of 100 proved cases of supratentorial brain tumors, the majority of which were accompanied with an obvious increase in their intracranial pressures (Table 4). Similarly, of the 85 patients of this group in whom there was an adequate visualization of both ventricles, bilateral ventricular dilatation (except in that portion of the homolateral ventricle immediately compressed by the tumor) was found in 70.

The explanation of an increased intracranial pressure in the presence of ample or incompletely collapsed ventricles whose channels connecting with the cisterna magna are not obstructed has not been clear on a simple space-consuming basis. On the other hand, an obliteration of space in the smaller and more susceptible subarachnoid spaces over the cerebral cortices, or a similar blockage of the cerebrospinal-fluid pathways at the incisura, seems entirely plausible and might well produce a progressively increasing pressure commensurate with the degree of absorptive block. This progression of changes is well illustrated in the following case history.

H. K., a white man aged 49, was admitted to the neurosurgical service of the University of California Hospital with a history of generalized convulsive seizures of seven-weeks' duration. Convulsions were initiated by clonic movements of the right hand. In addition, he had experienced several minor episodes, which consisted of twitching limited to the fingers of the right hand. Physical examination revealed a normal condition except for filling of the left optic cup, underactivity of the right lower part of the face, and increased deep reflexes in the right arm. Pneumoencephalographic study revealed slightly dilated ventricles, no shift of the

TABLE 4.—*Comparison of Ventricular Size in One Hundred Proved Cases of Intracranial Tumors**

Lateral Ventricles		Number
Neither dilated		9
Equally dilated		14
Both dilated; ventricle larger on side of tumor		21
Both dilated; ventricle larger on side opposite tumor		35
Ventricle dilated on side of tumor; ventricle opposite tumor normal		2
Ventricle opposite tumor dilated; ventricle on side of tumor normal		4
Unilateral filling		
(*a*) Ventricle on side of tumor filled only and dilated	(3)	
(*b*) Ventricle on side of tumor filled only and not dilated	(1)	
(*c*) Ventricle on side opposite tumor filled and dilated	(11)	15
		100

* Only those cases are included in which there was, as far as could be ascertained, a unilateral cerebral hemispheral involvement. Pneumographic study by means of ventriculography was performed in 80 of these cases.

ventricular system, dilated basal cisterns, and greatly dilated supracortical subarachnoid spaces. The roentgenographic diagnosis was "marked cortical atrophy," there being no findings to indicate the presence of a brain tumor. A three-hour follow-up roentgenogram showed only 10% of the gas still present.

The patient was placed under an anticonvulsant regimen; despite this, he experienced an increase in the frequency and severity of his seizures. Definite weakness of his right arm developed three months later, and he was admitted for restudy six months after his initial entry. Physical findings at this time included definite weakness of the right arm and an increase of all the deep reflexes on the right side, the physical status otherwise being essentially the same as on the previous examination. Another pneumoencephalographic study was performed and showed, as before, slightly dilated ventricles with no shift. However, the subarachnoid spaces, although still larger than normal, were strikingly less dilated than on the previous examination, even to the point of obliteration of some channels over the vertex on the left side (Fig. 6). A three-hour follow-up roentgenogram now showed approximately 50% of the gas still present. Although an atrophic process was considered the probable cause of his symptoms, because of the sharp focal onset of his convulsions, an osteoplastic craniotomy was performed in the left temporo-occipital area. Except for some arachnoidal adhesions, no pathological change was noted. The patient made a good recovery from the surgical procedure and was again discharged.

Because of further progression of his seizures and weakness, and, finally, the development of signs of increasing intracranial pressure, he entered Mount Zion Hospital two and one-half

months later and died within two weeks. Postmortem examination revealed discoloration, prominent gyri, and a firmer consistency of the cerebral tissues just behind the left central sulcus. A firm tumor, 3 by 5 cm. in size, was observed in the left parietal lobe. The tumor proved to be a meningofibroblastoma.

This case illustrates the vital role of the subarachnoid spaces in the maintenance of the cerebrospinal-fluid circulation and the dynamic equilibrium of the central nervous system. The marked enlargement of the subarachnoid spaces observed in the first pneumoencephalographic study disappeared concurrently with the growth of his tumor. Correspondingly, the residuum of gas present three hours after the pneumoencephalographic injection rose from a normal of 10%, in the initial study, to 50%, in the second study, done six months later, thus suggesting a gross delay in the cerebrospinal-fluid-absorptive mechanism going hand-in-hand with the obliteration of the subarachnoid spaces and the growth of the tumor.

If this concept of an absorptive-block mechanism in association with intracranial space-consuming processes is correct, one would expect no great discrepancy in the dilatation of the lateral ventricles, except as the ventricle on the side of the

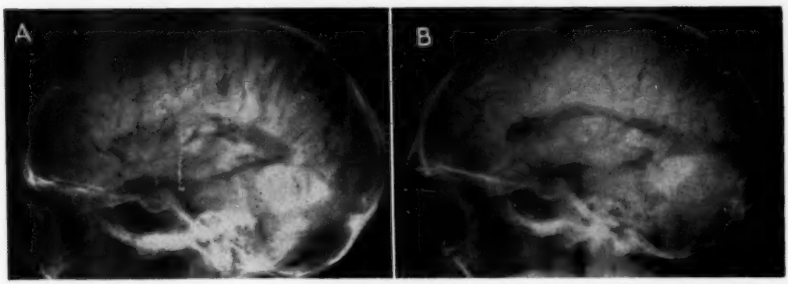

Fig. 6.—Right lateral projections. *A*, initial pneumoencephalogram; *B*, pneumoencephalogram six months later.

H. K., a man aged 49, had had Jacksonian seizures involving the right hand in the previous seven weeks, with progressive course. Physical and neurological examinations revealed an essentially normal condition except for filling of the left optic cup, underactivity of the right lower part of the face, and increased deep reflexes in the right arm.

The initial pneumoencephalographic study (*A*) revealed slightly dilated ventricles, no shift of the ventricular system, and greatly dilated supracortical subarachnoid spaces. The roentgenographic diagnosis was "marked cortical atrophy." A three-hour follow-up roentgenogram showed only 10% of the gas still present.

Further progression of his convulsive and neurological status in spite of anticonvulsant therapy led to his readmission six months later. Neurological findings at this time included weakness of the right arm and increased deep reflexes of the entire right side.

A repeat pneumoencephalographic study (*B*) showed a marked reduction in the size of the supracortical subarachnoid spaces. A three-hour follow-up roentgenogram showed 50% of the gas still present.

A negative exploration by osteoplastic craniotomy in the left temporo-occipital area was followed by further progression of his seizures and weakness, and, finally, by the development of signs of increasing intracranial pressure. He died three months later. Postmortem examination revealed a meningofibroblastoma in the left parietal lobe.

cerebral neoplasm might be directly distorted and compressed by the tumor. It was of interest to us in this connection that among the 85 cases of supratentorial tumors referred to previously (Table 4) in which an adequate visualization of both lateral ventricles was obtained, there were only 39 in which the ventricle contralateral to the tumor was the greater, while in the remainder the ventricles were equally dilated or the ipsilateral ventricle was the larger. These findings are contrary to

the old dictum that the dilatation of the ventricle contralateral to the tumor is noted so frequently as to be anticipated. They are, however, in keeping with the hypothesis suggested by this study, namely, that all space-obliterating processes, whether inflammatory or neoplastic in origin, may impair the cerebrospinal-fluid circulation and absorptive mechanism and result in an increase of intracranial pressure.

CONCLUSIONS

The dynamic equilibrium of the cerebrospinal fluid is controlled by the relative rates of formation and absorption of the cerebrospinal fluid. Abnormalities of the absorptive mechanism are most commonly found in clinicopathological conditions, since the usual margin of safety in the absorptive mechanism can compensate for all ordinary, and probably most abnormal, alterations in cerebrospinal-fluid formation. The commonest cause of an alteration in the hydrodynamic balance of the cerebrospinal fluid is to be found in processes which obstruct the absorptive bed or the subarachnoid channels leading to it.

Pneumoencephalography affords the best available method of study of the absorptive bed and the subarachnoid channels. The advantage of a combined procedure, involving a pneumoencephalographic injection directly following a ventriculogram, is suggested in those cases in which ventriculography is originally indicated, but in which it fails to reveal the lesion or point of obstruction of the cerebrospinal-fluid circulation.

The characteristic roentgenographic picture associated with an absorptive block consists of small or obliterated subarachnoid spaces and large "normal" or dilated ventricular spaces. These findings, in combination with a delay in the rate of absorption of a gas, such as ethylene (of high solubility in an aqueous solution), following its pneumoencephalographic injection, form a triad characteristic of an absorptive block.

Such a pneumoencephalographic study with ethylene and oxygen gases is reported for 630 patients. A delayed or borderline disappearance of the gas was observed in 56% of patients with a history suggestive of meningoencephalitis and in 47% of patients with brain tumors. Only 16% of patients in the group with "idiopathic" epilepsy, most of whom showed a normal pneumoencephalogram or atrophic changes, had a delay in the rate of absorption of the gases. These findings, and other factors which are discussed, led to the conclusion that the rate of disappearance of ethylene after its pneumoencephalographic injection is a relatively sensitive test of a partial obstructive process and is capable of indicating such partial obstructions even before an impairment of cerebrospinal-fluid circulation, with a consequent increase of intracranial pressure, has occurred.

The fact that this triad of signs was observed in a significant number of patients with brain tumors suggests a common absorptive-block mechanism for all space-consuming and inflammatory lesions of the central nervous system. The explanation of increased intracranial pressure in the presence of dilated and unobstructed ventricles has not been clear on a simple space-consuming basis. An alternate mechanism suggested by this study, whereby space-obliterating processes (either inflammatory or neoplastic) may produce subarachnoid block, impairment of cerebrospinal-fluid circulation, and increased intracranial pressure, is presented and discussed.

Abstracts from Current Literature

Physiology and Biochemistry

CENTRAL NERVOUS CONTROL OF RHYTHMIC VARIATIONS OF BLOOD PRESSURE. B. P. BABKIN and W. C. KITE JR., Am. J. Physiol. **161**:92 (April) 1950.

The blood pressure in dogs may undergo rhythmic variations. The waves thus formed have different amplitudes and durations and are due to different factors. It is necessary to discriminate between (1) pulse waves, (2) respiratory waves, (3) waves originated by periodic contractions of the spleen and intestine, (4) short Traube-Hering waves appearing during asphyxiation in vagotomized animals, and (5) nonasphyxial waves of medium duration (average, 20 sec.) due to the periodic discharge of the vasomotor center of the brain stem.

The nonasphyxial waves, of the last category, which were studied in this work, could be obtained easily under chloralose-urethan anesthesia. They were inhibited by pentobarbital. Electrical stimulation of the anterior sigmoid and coronal gyri produced an increase in the blood-pressure waves. The effect obtained by stimulation of the anterior composite gyrus was more constant and usually showed a diminution in the amplitude of these waves. However, in some instances, augmentation took place. No prolonged effect was obtained by stimulation of the anterior cingulate gyrus.

The results of ablation showed that the cortical control of nonasphyxial blood-pressure waves lies in the frontal lobe close to the sensorimotor region, although it could not be placed with certainty in the premotor region. Intercolliculomesencephalic section of the brain stem produced a further increase in amplitude, and in some instances a slight increase in rate, of the nonasphyxial blood-pressure waves. This indicated that section of the brain stem removed a regulating mechanism for the vasomotor center more important than that found in the cerebral cortex. Experiments with removal of the hypothalamus suggested that this regulating mechanism is located in that part of the brain.

ALPERS, Philadelphia.

Neuropathology

MULTIPLE CYSTIC SOFTENING OF THE BRAIN IN THE NEWBORN. C. E. LUMSDEN, J. Neuropath. & Exper. Neurol. **9**:119 (April) 1950.

Interpretation of some of the problematical cases of infantile encephalomalacia in the literature is rendered difficult because there is no clear-cut information regarding the presence or absence of injury to the brain at birth.

Lumsden reports a case of "disseminated encephalomalacia with multiple cavity formation." There was no history of cerebral birth injury or of asphyxia neonatorum, and careful anatomical study disclosed no vascular injury or thrombosis.

The author gives reasons for rejecting Marburg and Casamajor's hypothesis that these, and allied, forms of encephalomalacia (including Schilder's disease, or progressive subcortical encephalopathy) in the newborn and in young infants are due solely to phlebothrombosis and phlebostasis in the Galenic system and are caused by cerebral birth injury. He draws attention to the possible role of transsynaptic degeneration and the much greater ferment activity in the production of malacia in degenerative disease of the central nervous system of the infant.

The suggestion is offered, from this study, that damaged myelin itself liberates a lytic ferment, the activity of which, in most pathologic processes, is neutralized or checked in some way by the action of the oligodendroglia. If the oligodendrocytes were primarily diseased or defective, the inhibitory action of these cells upon the myelin ferment might be lost or impaired, so that myelinolysis could spread relatively unimpeded. Such a mechanism could account for the specific histopathologic features of the primary demyelinating diseases.

ALPERS, Philadelphia.

NEUROPATHOLOGICAL CHANGES IN NITROGEN TRICHLORIDE INTOXICATION OF DOGS. J. H. LEWEY, J. Neuropath. & Exper. Neurol. **9**:396 (Oct.) 1950.

Nitrogen trichloride, commercially called agene,* was used in most wheat-consuming countries to bleach and soften wheat flour. This substance has been found to be toxic to dogs, rabbits, and ferrets, but not to the monkey, cat, guinea pig, or man. Dogs when on a diet rich in nitrogen trichloride-treated flour become atactic within a few days and exhibit running fits. Electroencephalographic records of these dogs suggest that these fits are epileptoid in character.

Lewey found that the pathological changes in the central nervous system in such dogs are characterized by a patchy liquefaction necrosis in the deeper layers of the cerebral cortex and of the U-fibers, extending slightly into the white matter. These changes are widespread in the cerebral cortex, but most pronounced in the hippocampus. Severe changes of a different character are observed in the cerebellum, specifically in the Purkinje cells and their afferent and efferent fibers, and in the interconnecting system of the basket cells and their prolongations. Milder alterations are noted in the nerve cells of the dentate and the roof nuclei.

Nitrogen trichloride is no longer employed and has been replaced by chlorine dioxide (ClO_2), which is harmless even for dogs.

ALPERS, Philadelphia.

Meninges and Blood Vessels

CLINICAL SYNDROME OF OCCLUSION OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY. B. LEVINE, L. J. CHESKIN, and I. L. APPLEBAUM, Arch. Int. Med. **84**:431 and 439 (Sept.) 1949.

The authors report three cases of the syndrome associated with occlusion of the posterior inferior cerebellar artery. The onset is usually sudden without loss of consciousness, but with a feeling of dizziness. The patient falls toward the side of the lesion; nystagmus is present, together with difficult deglutition, a homolateral Horner syndrome, ataxia, trigeminal analgesia and thermanesthesia, and contralateral analgesia and thermanesthesia of the body.

The symptoms are due to a highly localized lesion involving the lateral portion of the medulla, which includes the nucleus ambiguus, Deiters' nucleus, the descending root of the fifth nerve, the lateral spinothalamic tract, the medullary sympathetic center, the direct spinocerebellar tract, the restiform body, and, occasionally, the nucleus facialis.

The authors, as well as others who have studied this syndrome, stress the absence of loss of consciousness, in contradistinction to its occurrence in other forms of cerebrovascular accidents.

Arteriosclerosis is the most important etiologic factor. Hypertension seems to play an equally important role in the pathogenesis of this syndrome. Syphilitic arteritis and metastatic neoplasia are known to have produced this syndrome on occasion.

In the differential diagnosis, one must consider occlusion of the vertebral artery, the anterior spinal artery, and the artery of the lateral recess. The absence of signs of involvement of the pyramidal tract excludes the possibility of involvement of the vertebral artery. The anterior spinal artery is a branch of the vertebral artery and supplies the central and anterior portions of the medulla, including the pyramids. It is obvious, therefore, that occlusion of that vessel would also lead to signs in the pyramidal tract, thus differentiating the lesion from that of the syndrome of the posterior inferior cerebellar artery. The artery of the lateral recess supplies an extremely small, localized area in the medulla and in no way gives the classic picture of the Wallenberg syndrome.

The immediate therapy concerns itself with the maintenance of nutrition. It may be necessary to feed the patient parenterally or by passage of a tube into the stomach. In the presence of syphilis antisyphilitic therapy is indicated. The use of anticoagulant therapy in cases of this syndrome is a controversial issue.

Aspiration pneumonia is common, and appropriate antibiotic therapy should be instituted. The prognosis with regard to life and the return of essential functions is generally good. The ataxia and inability to swallow often improve after several months. It must be remembered, however, that the syndrome is an indication of more generalized vascular disease, in which sudden death is not uncommon.

GUTTMAN, Wilkes-Barre, Pa.

Diseases of the Brain

FIXATION OF THE VOCAL CORDS IN ACROMEGALY. J. K. GROTTING and J. DEJ. PEMBERTON, Arch. Otolaryng. **52**:608 (Oct.) 1950.

Grotting and Pemberton reviewed 453 cases of acromegaly. In only 65 cases were laryngeal examinations made, and in seven of these cases fixation of the vocal cord was noted. They review these seven cases in detail as evidence that in some cases fixation of the vocal cords should be included as part of the picture of acromegaly.

In five of the seven cases nearly complete bilateral fixation of the vocal cords had occurred; in one case there was partial bilateral fixation of the cords, and in one case one cord was fixed in the position of complete abductor paralysis. The etiologic factor is not certain. Paralysis of the recurrent laryngeal nerve through stretching by overgrowth of the cartilaginous structure is a possibility, as is interference with the movement of the cricoarytenoid joint. Tissue overgrowth or cartilage enlargement might serve to limit the motion of the joint.

The authors point out that the vocal cords of all patients who have acromegaly should be examined before operation, as should those of any such patients whose presenting symptom is dyspnea or hoarseness.

ALPERS, Philadelphia.

RADIOACTIVE DIIODOFLUORESCEIN IN DIAGNOSIS AND LOCALIZATION OF CENTRAL NERVOUS SYSTEM TUMORS. L. DAVIS, J. ARTIN, M. ASHKENAZY, G. LEROY, AND T. FIELDS, J. A. M. A. **144**:1424 (Dec. 23) 1950.

Radioactive diiodofluorescein was used in the study of 200 cases of a diagnosed space-occupying lesion of the central nervous system. The observations were correlated with the preoperative clinical diagnosis; with the electroencephalographic, pneumographic, and angiographic findings, and with observations at operation and autopsy. Postoperative and postirradiation tests were made, and the results of all these studies were correlated with the histopathologic characteristics of the tumors.

In the 200 cases, there was 91% accuracy in localization of the 95 histologically verified space-occupying lesions of the central nervous system. A positive result in the radioactive dye test was recorded in 5 of the 6 verified tumors of the spinal cord. The affinity of radioactive dye for tumor tissue was related to the cellularity and vascular pattern of the tumor. The more malignant the neoplasm, the greater was the concentration of radioactive fluorescein.

The negative results also proved to be 95% accurate and were of equal importance in the differentiation of cerebral neoplasms, especially from such lesions as hypertensive cerebrovascular accidents, perichiasmal arachnoiditis, meningovascular syphilis, and intracranial aneurysms.

Localization by the radioactive-dye method proved to be much more precise than localization by electroencephalography or pneumography, whenever verification was obtained surgically or at autopsy. The authors believe that the radioactive-diiodofluorescein-tracer test is a simple, safe, painless, and reliable method for the localization and diagnosis of brain tumors, and one which should gain in value as more sensitive detection equipment and more specific radioactive dyes become available.

ALPERS, Philadelphia.

MEDULLOBLASTOMA. N. RINGERTZ and J. H. TOLA, J. Neuropath. & Exper. Neurol. **9**:354 (Oct.) 1950.

Ringertz and Tola report the pathologic and clinical features in 111 cases of medulloblastoma. On the basis of localization, there were three groups. In the first, the midcerebellar-posterior (89 cases), the tumors grew in the caudal part of the vermis, behind the fastigium, and extended into the cerebral hemispheres. The second group, midcerebellar-anterior (6 cases), consisted of tumors scarcely mentioned by previous authors. These tumors were connected with the anterior medullary velum but did not extend behind the fastigium. In the third, the lateral, group (16 cases), the tumor grew in the cerebellar hemispheres in 13 cases and was localized in the cerebellopontile angle in the other 3 cases.

A study of the stroma structure led the authors to the conclusion that the solid part of most of the medulloblastomas is to a large extent formed by coalescing arachnoidal infiltrates. This agrees with the concept that remnants of the external granular layer often are the site of origin

of the growths. This is especially true of the laterally located tumors, exclusive of those in the cerebellopontile angle. The mode of origin of the midcerebellar tumors is obscure, either the external granular layer or an embryonal residue in the medullary velum being considered a probable source.

Of the 111 patients, 71 were males and 40 females—a ratio of approximately 2:1. The average age of the patients in the lateral group was 17 yr.; it was 13.8 yr. for the entire material. Symptoms began more or less abruptly and progressed until the patient became completely helpless.

Radical extirpation was carried out in 42 cases; nonradical extirpation, in 50 cases, and biopsy only, in 9 cases. In 6 cases the tumor was not found on surgical exploration, but its presence was verified at autopsy. Roentgen therapy was consistently given after operation.

Except for four patients who are still living, practically all the patients have died of recurrences. The longest postoperative survival has been 64 mo. The average postoperative survival time in this series was 16.4 mo.

ALPERS, Philadelphia.

EPIDERMOIDS: CLINICAL EVALUATION AND SURGICAL RESULTS. F. C. GRANT and G. M. AUSTIN, J. Neurosurg. **7:** 190 (May) 1950.

This paper deals with the surgical treatment and results of a group of 22 patients with epidermoid tumor of the brain.

Headache was the predominant symptom in 14 of these patients, and visual disturbances were the next commonest complaints.

All the 7 patients with extradural epidermoids showed roentgenologic changes of the skull typical of this type of tumor. Of the 15 intradural tumors, 14 could not be diagnosed preoperatively from the roentgenographic appearance.

The extradural group of tumors showed a preoperative duration of symptoms averaging 2.9 yr., as compared with an average duration of 4.6 yr. for the intradural group.

The commonest sites of occurrence of the intradural group were the cerebellopontile angle and the parapituitary region, with 4 occurring in each position. Four of the 7 extradural and 4 of the 15 intradural tumors were completely removed, with an over-all mortality of 22.7%.

ALPERS, Philadelphia.

MENINGIOMAS OF THE CEREBELLAR FOSSA. A. D'ERRICO, J. Neurosurg. **7:** 227 (May) 1950.

Ten cases of meningioma of the cerebellar fossa are reported. In these cases certain characteristic features were found which could have led to a much earlier diagnosis, when the tumor would have been smaller and more amenable to complete removal.

It appears from a study of the findings that the site of attachment determines the symptoms to a large extent. The most consistent findings, and one of the earliest, was the pain in the back of the head and neck. This was usually of long standing, and in one case was present for 17 yr.

These lesions are slow in growth, and even with incomplete removal the patient has a long survival period. In this series, in addition to two postoperative fatalities, there was one death three and a half years after the second operative stage. Although complete extirpation of large tumors, even with invasion of the lateral sinus or tentorium, can be accomplished, diagnosis at an early stage is important, since a complete removal should then be the rule, with little, if any, disability remaining.

Histologic study of these tumors shows a high proportion of the fibrous and meningothelial types. Only two psammomas were in the series.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

MUSCLE WEAKNESS AND WASTING IN SCIATICA DUE TO FOURTH LUMBAR OR LUMBOSACRAL DISC HERNIATIONS. E. KUGELBERG and I. PETERSEN, J. Neurosurg. **7:**270 (May) 1950.

Sixty-six patients with sciatica due to herniation of the fourth lumbar (41 cases) or lumbosacral (25 cases) disk, verified by operation, were examined by Kugelberg and Petersen for muscular disturbances in the lower leg and foot.

In 90% of the cases of herniation of the fourth lumbar disk the muscles within the extensor group were affected, with the following distribution: extensor digitorum brevis, 85% (atrophy

or a palpably soft consistency on maximal contraction); extensor hallucis longus, 46% (weakness), and tibialis anterior, 41% (weakness). In 13% of the cases there was weakness of the muscles of the flexor group. In these cases there were also disturbances of the extensor group.

In only 16% of the cases of herniation of the lumbosacral disk were the muscles affected, with weakness and wasting of the extensor group in 8% and of the flexor group in 8%.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

THE NON-INFECTIOUS NATURE OF THE GUILLAIN-BARRÉ SYNDROME WITH A POSSIBLE EXPLANATION FOR THE ALBUMINO-CYTOLOGICAL DISSOCIATION. N. REITMAN and K. ROTHSCHILD, Ann. Int. Med. **32**:923 (May) 1950.

The Guillain-Barré syndrome is a clinical entity which is not often diagnosed, although its occurrence is not uncommon. The chief reason for this is the failure of all attempts to isolate an etiologic agent and the multiplicity of synonyms by which this form of neuritis is known.

Reitman and Rothschild report two cases fulfilling the criteria of the Guillain-Barré syndrome which are unusual in that they do not represent postinfectious phenomena. In one case the cause was bronchogenic carcinoma with metastases to the extradural fat, compressing the spinal cord and nerve roots from the seventh cervical to the eighth thoracic. The second case represents an unusual form of serum sickness following injection of tetanus antitoxin. This case showed most extensive neurologic involvement, with rapid and practically complete recovery.

The authors suggest a common anatomic basis for the Guillain-Barré syndrome, regardless of the etiologic agent. It is believed that the basic pathologic process consists in an obstruction to the perineural circulation of the cerebrospinal fluid as the nerve roots emerge from the cord, permitting absorption of fluid and electrolytes but preventing the absorption of the larger protein molecules. The characteristic albuminocytologic dissociation may be explained in this fashion.

ALPERS, Philadelphia.

RESPIRATORY MANIFESTATIONS OF DORSAL SPINE RADICULITIS SIMULATING CARDIAC ASTHMA. D. DAVIS, Ann. Int. Med. **32**:954 (May) 1950.

The purpose of the present communication is to show that respiratory distress may be the only, or major, manifestation of radiculitis involving the thoracic nerves and may sometimes simulate attacks of cardiac asthma. The three patients reported here were thought to have cardiac dyspnea before the spinal origin of the symptom was established.

The mechanism of the symptom is not known. Motor involvement, however, with muscle spasm is very common in irritation of the cervical nerve roots, and patients with involvement of the thoracic portion of the spine likewise frequently show spasm of muscles of the chest wall. It is probable, therefore, that the respiratory symptoms are in some way related to spasm of the accessory muscles of respiration.

The recognition of the spinal origin of this symptom will not be difficult if its possibility is entertained in differential diagnosis. The final diagnosis, however, must be based on positive evidence of irritation of nerve roots. A history of chest pain with radicular characteristics; the relation of respiratory distress to a given bodily position, such as reclining or sitting; costochondral and thoracic-spinal tenderness; the reproduction of symptoms by pressure over the thoracic vertebrae; roentgenologic evidence of hypertrophic arthritis of the spine, and, particularly, the therapeutic response to traction and other orthopedic measures will lead to a correct diagnosis in most instances.

ALPERS, Philadelphia.

INFECTIOUS MONONUCLEOSIS AND POLYNEURITIS. N. E. CREATURO, J. A. M. A. **143**: 234 (May 20) 1950.

Creaturo reports the case of a high-school girl aged 17 with typical infectious mononucleosis. The neurologic manifestations were those of polyneuritis of the Guillain-Barré type, as evidenced by the multiple involvement of peripheral nerves and an ascending type of paralysis, with a high protein content of, and no cells in, the spinal fluid.

With the usual supportive measures—administration of vitamins, active and passive exercises, and physical therapy, the patient improved up to a certain point, and then her progress ceased. The condition of her legs did not improve until administration of dimercaprol injection U. S. P. was started, from which time improvement was rapid. Three and one-half months after the onset of illness no paralysis was present, and the patient was able to attend school full time and, in addition, to work part time as a salesgirl.

Creaturo believes that this case may help to support the theory proposed by Furmanski, namely, that initially neuropathies are reversible biochemical disorders of the neuron, that no structural changes of degeneration occur, and that dimercaprol has the ability to restore disrupted cellular metabolism by its action on the enzyme system.

ALPERS, Philadelphia.

UNILATERAL DEAFNESS AND PROGRESSIVE FACIAL PALSY DUE TO INTRAPETROUS NEUROFIBROMA. J. GRAFTON LOVE, Proc. Staff Meet., Mayo Clin. **25**:228 (April 26) 1950.

Love reports the case of a girl aged 16 with deafness in the right ear of eight-years' duration and progressive paralysis of the right side of the face for two and one-half years. The roentgenologic picture was that of an intrapetrous epidermoid. At operation the tumor was found entirely within the petrous bone. It proved to be a neurofibroma, very fibrous in type. Presumably, the tumor had taken its origin from the eighth cranial nerve within the petrous bone, and it never at any time presented in the cerebellopontile angle, as tumors of the eighth nerve usually do.

The facial paralysis and loss of hearing were unaltered by operation. One month after the first operation a spinofacial anastomosis on the right side was carried out. Three months later there was no definite clinical evidence of reinnervation except for possible slight movement about the right corner of the mouth and below the nose. Fourteen months later there was pronounced improvement, with movement of all facial muscles, including the forehead.

ALPERS, Philadelphia.

Treatment, Neurosurgery

USE OF PHENYLACETYLUREA (PHENURONE*) IN CONVULSIVE DISORDERS. S. C. LITTLE and R. R. MCBRYDE, Am. J. M. Sc. **219**:494 (May) 1950.

Phenacemide (phenurone*) was administered to 32 patients with a convulsive disorder.

The improvement in the number of seizures as compared with that for the best prior treatment was as follows: grand mal, 54%; psychomotor, 66%. Some of the improvement in the grand mal seizures could be attributed to other medications, but phenacemide appeared to be responsible for most of the improvement in psychomotor seizures.

The relative maximal improvement occurred within the first two months after administration of phenacemide was begun, and with doses of 2.0 gm. a day or less. Toxic symptoms, chiefly referable to the central nervous system or the gastrointestinal tract, occurred in many cases, but necessitated discontinuance of the drug in only 16%.

Little and McBryde conclude that phenacemide appears to cause considerable improvement in psychomotor disorders, slight improvement in grand mal seizures, and little or no improvement in petit mal, tonic, and myoclonic type seizures.

ALPERS, Philadelphia.

INTRAVENOUS NEOSTIGMINE IN DIAGNOSIS OF MYASTHENIA GRAVIS. J. E. TETHER, Ann. Int. Med. **29**:1132 (Dec.) 1948.

Tether describes a diagnostic method which may be employed with patients who are suspected of having myasthenia gravis. He recommends the injection of 0.5 mg. of neostigmine methylsulfate intravenously, instead of 1.5 mg. intramuscularly, the latter being the method originally described by Schwab and Viets. Neostigmine has been administered intravenously to several hundred patients, both myasthenic and nonmyasthenic, without serious untoward reactions. The author states that intravenous administration of neostigmine has the following advantages over the intramuscular route as a diagnostic test: (1) It gives a more rapid com-

plete response, thus lessening the possibility of a false-negative diagnosis in a mild case; (2) only objective responses need be considered, thus decreasing the risk of a false-positive diagnosis; (3) the quick, clear-cut response should facilitate office diagnosis by a busy practitioner and aid in demonstration of cases for teaching purposes.

If the history and physical findings are sufficiently characteristic of myasthenia gravis, 1 cc. of a 1:2,000 solution of neostigmine methylsulfate (0.5 mg.) is injected intravenously within a timed one-minute period. Improvement in a true case of myasthenia gravis often begins before the needle can be withdrawn and is usually maximal in, at most, five minutes. The performance test may then be repeated after five minutes have elapsed, and the degree of objective improvement is noted and recorded. Occasionally, in a case of very mild true myasthenia gravis, the response to an intravenous dose of 0.5 mg. of neostigmine methylsulfate is doubtful or minimal. In such a case this procedure should be repeated on the following day with 1 mg., provided there were no untoward reactions to the 0.5-mg. dose.

Atropine sulfate, usually 0.6 mg., should always be kept at hand and should be injected subcutaneously whenever side effects become manifest, but is never to be injected with neostigmine, according to Tether. It is stated that the side effects, when they do occur, are uncomfortable, but apparently not dangerous; and Tether does not, as Viets advises, use atropine simultaneously with neostigmine to offset them.

GUTTMAN, Wilkes-Barre, Pa.

EXPERIMENTAL KLEBSIELLA MENINGITIS TREATED WITH INTRATHECAL AND INTRAMUSCULAR STREPTOMYCIN. G. ZUBROD, Bull. Johns Hopkins Hosp. **84**:461 (May) 1949.

Zubrod attempts to answer the question, "Is it necessary for the successful treatment of meningeal infection to effect inhibitory concentrations of the chemotherapeutic agent in the cerebrospinal fluid?" In this study, a meningitis using Klebsiella pneumoniae as the infecting organism was employed. Meningitis was induced by intracisternal injections in the cats.

As a result of these studies, it appears that treatment by means of intrathecal or intramuscular administration of streptomycin, or by combined injections, suggests that survival of the cats is governed by the amount of drug that reaches the cerebrospinal fluid. Cats that were given a sufficient amount of streptomycin by the intramuscular route survived.

Zubrod states that in the treatment of meningitis with drugs that are not readily transferred from the plasma to the cerebrospinal fluid, intrathecal injection in the lumbar area is probably an inefficient way of getting the drug into the infected area. It would seem more desirable to accomplish the transfer of the drug from the blood to the cerebrospinal fluid. The efficacy of this mode of administration of antibiotics for the effective management of clinical meningitis, when it is compared with that of intrathecal injections, can be determined only by the clinical study in patients.

GUTTMAN, Wilkes-Barre, Pa.

PREVENTION AND TREATMENT OF MOTION SICKNESS. L. E. GAY and PAUL E. CARLINER, Bull. Johns Hopkins Hosp. **84**:470 (May) 1949.

Gay and Carliner report the results of their studies on the administration of dimenhydrinate "dramamine."

During a 10-day sea voyage, dimenhydrate was administered to 389 persons who suffered from seasickness. Of this number, 372 were completely relieved of symptoms within one hour after the first dose, of 100 mg. Seventeen persons derived only partial benefit or no relief. It was found that a dose of 100 mg. prescribed to be taken every five hours and before retiring was adequate to control the most distressing symptoms. When the patient was unable to retain a capsule, rectal administration proved effective. The benefit derived by this route was as rapid and as complete as that derived by the oral route. No untoward reactions to dimenhydrinate were encountered by any soldier who received the drug.

The action of dimenhydrinate on the prevention and control of motion sickness is not yet definitely established. Studies are in progress to attempt to explain the mechanism.

GUTTMAN, Wilkes-Barre, Pa.

HAEMOPHILUS INFLUENZAE MENINGITIS TREATED WITH STREPTOMYCIN. E. C. ALLIBONE, J. D. PICKUP and K. ZINNEMANN, Lancet **1**:610 (March 17) 1951.

The authors report on the treatment of 11 infants with Hemophilus influenzae meningitis, all under 2 years of age. All received streptomycin intramuscularly, and 10 of the 11 were given the drug intrathecally as well. Eight received penicillin intramuscularly, in addition to the streptomycin, and seven were given penicillin intrathecally. The sulfonamide drugs were also tried with six of the 11 infants.

In all cases the strains of H. influenzae isolated were of type B. No streptomycin-resistant strains developed.

Seven of the patients were reported as cured; three died, and one had dementia, blindness and hydrocephalus. Autopsy of the infants who died revealed a tenacious, yellow-green pus covering both cerebral hemispheres and encasing the spinal cord. In one of the cases the exudate was bacteriologically sterile.

The authors indicate that one of the chief difficulties in treatment of this condition is early establishment of diagnosis, since often the presenting symptoms do not suggest meningitis but may be a gastrointestinal disturbance or convulsions, attributed to teething. Earlier diagnosis by lumbar puncture is essential if the results are to be improved.

MADOW, Philadelphia.

SURGICAL TREATMENT OF EPILEPSY: SUBPIAL RESECTION OF EPILEPTOGENIC FOCUS. G. H. DICKMANN, Prensa méd. argent. **35**:709 (April 16) 1948.

The electroencephalogram has made possible rapid strides in the study and treatment of epileptogenic foci. The epileptogenic focus has been shown to be in the cerebral cortex around the scar, but not within it. The fundamental principle in treatment is the removal of the cortex around the cicatrix. Indications for treatment are symptomatic epilepsy due to a tumor, cyst, or abscess; traumatic epilepsy which is refractory to adequate medical treatment, and epilepsy which does not respond to treatment and which is associated with abnormal electrical discharges from the resectable part of the cerebral cortex. Any part of the right cerebral hemisphere may be resected except for the calcarine zone and parts of the motor area; in the left hemisphere, the posterior two-thirds of the temporal lobe, the inferior half of the parietal lobe, and the occipital lobe should not be resected. In traumatic cases in which homonymous hemianopsia exists, the occipital lobe, or part of it, may be removed. The author notes the importance of conserving the pial covering over the part of the cortex removed. He confirms the observations of others that a considerable amount of the motor cortex can be removed, with good recovery. The white substance is usually spared, and the area to be resected is suctioned. Continuous anticonvulsant medication is advised for a while, with subsequent gradual decrease in dosage. Fifteen cases are reported. In 7 the epilepsy was of traumatic origin; in 1 case it followed operation for a post-tonsillectomy cerebral abscess, and in the rest the cause was unknown. One patient could not be followed. Three patients had had no attacks after the operation. One patient showed extraordinary improvement; eight, a considerable improvement, and two, definite, though slight, improvement.

N. SAVITSKY, New York.

THERAPY OF MENINGITIS CAUSED BY BACTERIUM COLI IN SUCKLING INFANTS. E. GRUNDLER, Arch. Kinderh. **138**:43, 1949.

Grundler reports two cases of meningitis caused by Escherichia coli, in an infant aged 8 weeks and in another aged 10 weeks. The younger infant was given 12,000 units of penicillin every three hours by the intramuscular route (total 1,500,000 units), followed by 100,000 units by the intrathecal route. Penicillin therapy was combined with oral administration of sulfathiazole and a mixture of equal parts of sulfamerazine and the 4-aminomethylbenzene sulfonamide salt of sulfathiourea. The older infant was given two courses of penicillin, with a total of 2,400,000 units, by the intramuscular route and 140,000 units by the intrathecal route. Penicillin was combined with oral administration of sulfonamide compounds. Streptomycin was administered in doses of 0.1 Gm. twice daily by the intrathecal route during the interval between the two courses of penicillin. Both infants made a complete recovery. The result is noteworthy because in vitro penicillin seems to have no effect or to affect only certain strains of Esch. coli. There is also the possibility that the salutary results were due to the sulfonamide compounds and to the intrathecal therapy.

J. A. M. A.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

LEWIS D. STEVENSEN, M.D.

President, New York Neurological Society, Presiding

Combined Meeting, March 14, 1950

Electrostimulatory Therapy as Immediate Antidote for Barbiturate Poisoning. Dr. Theodore R. Robie.

When certain psychoses and neuroses are treated with unidirectional-current cerebral electrostimulation (nonconvulsive), in which thiopental-sodium anesthesia is necessary, the author noted immediate awakening after treatment. This observation suggested the use of the method in thwarting suicidal attempts by intentional ingestion of an overdose of "sleeping tablets." This method of treating barbiturate poisoning has been found efficacious and successful by a number of psychiatrists. Others will be astonished at the simplicity of the procedure, the ease of administration, the increased number of successes that can be expected as compared with chemical-antidote therapy, and the relative rapidity of return to consciousness from the chemically self-induced coma.

Patients thus resuscitated can then be given convulsive electroshock therapy to dispel the melancholia which precipitated the suicidal attempt, with the expectation of a successful outcome in 80 to 90% of cases.

The technique of administering cerebral electrostimulation is easily acquired by observing the treatment given by any one of the many psychiatrists now using the Reiter CW47 apparatus. The dose applied is ordinarily from 3 to 1 ma. but may be raised, if necessary, for deeply narcotized subjects.

DISCUSSION

Dr. Lewis D. Stevenson: This is one of the most interesting and important papers that has been presented before this Society in a long time. It is practical, and the method works.

Dr. Lothar B. Kalinowsky: I have not tried the treatment described by Dr. Robie, but the clinical evidence is convincing. It shows again how clinical observations often lead to the discovery of new therapeutic measures. Dr. Robie said that the diencephalon was stimulated. I wonder whether he assumes that in all present methods of electrical stimulation of the head the current reaches the diencephalon or whether he uses a special application of the electrodes. Furthermore, is there any evidence that the usual alternating current cannot be used for the electrostimulation in the same way as the unilateral current? We are used to consider the effect in electroshock treatment as caused by the convulsion. Dr. Robie stated that in this nonconvulsive treatment a deep pentobarbital-sodium narcosis was used and that the effect did not seem to be the same as that in convulsive treatment. I wonder, therefore, whether the effect produced by the combination of nonconvulsive electrostimulation and barbiturate narcosis was not actually a prolonged narcosis, similar to that which can be achieved with barbiturates. Only if, for example, in simple depressions the same recovery could be obtained with three or four applications of nonconvulsive treatment would we have to reconsider our theoretical concept of electric-convulsive treatment.

Dr. Irving J. Sands: In 1923 I published an article on barbital intoxication, presenting a series of patients from the psychiatric division of Bellevue Hospital (Barbital [Veronal] Intoxication, *J. A. M. A.* **81**:1519-1921 [Nov. 3] 1923). Since the introduction of the law making it mandatory for the pharmacist to dispense the barbiturates only on a physician's prescription, there has been a decided decrease in the number of cases of barbiturate poisoning. However, there are still too many such cases; I see about three or four a month. One of the most

important and interesting, and almost specific, signs that I have encountered in this condition is the spontaneous contraction and dilation of the pupils. In the necropsy material no specific changes have been observed. I have used caffeine, nikethamide, metrazol® (pentylenetetrazole), and picrotoxin in the treatment of barbiturate poisoning. I have never used the method described by Dr. Robie, but I shall certainly try it with the next patient who may be under my care. It impresses me as a simple, practical, and very effective method, apparently saving the lives of many who would die under the older forms of treatment.

DR. LEWIS D. STEVENSON: Dr. Robie, will you tell us the difference between the orthodox treatment machine and the machine you use in electrostimulatory therapy?

DR. THEODORE R. ROBIE: The dose is much smaller, and the voltage is minimal with the electrostimulator.

DR. LEWIS D. STEVENSON: What is the voltage?

DR. THEODORE R. ROBIE: It is never over 15 volts, and it is usually from 7 to 7.5 volts. With the orthodox machine it is from 90 to 130 volts, or even up to 145 volts, and a good deal of confusion and memory defect are encountered with the larger voltage. While there is none from the machine I use, I do not want this paper to be misconstrued as a plea for electrostimulatory therapy for the psychoses or as an attack on electroshock therapy per se. Dr. Gerhard Hershfeld will present a paper at the annual meeting of the American Psychiatric Association in which he gives the present indications for the use of electrostimulatory therapy instead of electroshock therapy (*Psychiat. Quart.*, Supp., Pt. 2, 1950).

I should like to point out one or two things. Picrotoxin sufficient to produce an adequate opposing effect against the barbiturate would poison the patient. In poisoning the patient, one may produce convulsions; then one must give barbiturates to abolish the status produced with the picrotoxin, and perhaps the patient will be set back in the same state of barbiturate coma as before, which may carry him into bronchopneumonia, and this, in turn, may carry him off. Deaths from barbiturate coma result from respiratory paralysis unless the patient lives long enough to die of bronchopneumonia. One does not have to observe this treatment more than two seconds to know the truth of what I am saying. One can see the improvement in the respirations the second one turns the machine on. The increased amplitude of respiration and the increased ventilation are apparent. From our observations we have suspected that barbiturates are being eliminated through the expired air. Many persons have called attention to the particular odor of the breath of many patients who are being treated for psychoses or neurosis with the stimulatory method, and we give barbiturates intravenously to these patients.

In answer Dr. Kalinowsky: I do not believe that the beneficial effect of electrostimulatory therapy can be due to the prolonged pentobarbital-sodium effect, for it is not prolonged. If the patient is given 5 to 7 grains (0.30 to 0.45 gm.), he will wake up in two minutes, and he will not wake up that soon ordinarily. If he wakes up and talks after five minutes of stimulation, he does not have any recollection of the treatment. In rare instances, before I turn off the stimulator, I hear them make guttural sounds. Wilcox is using this method for his psychopenetration. One can suggest things to the patient under stimulation which he will repeat afterward; one can say to him, "You are feeling better," and when he wakes up he will repeat, "I am feeling better."

The question was asked whether the effect is due to stimulation of the diencephalon. I would rather not go into that. Hershfeld, however, is convinced that it is.

I should hesitate to use the old machine for this form of treatment, for the amount of cerebral irritation from this minimal dose of less than 7 volts is itself terrific, and the stimulation from the Rahm or the Offner machine would be infinitely greater. In my opinion, the patient could not withstand it, even if given a massive dose of thiopental. In the case of a patient treated only yesterday we gave 5 cc. of thiopental sodium, thinking that we had her well anesthetized, but with a current of only 2.5 ma. she was moving about and almost off the table. So we stopped and gave 3 cc. more thiopental sodium and could then proceed with the treatment. I do not think you can produce any effect with the earlier machine, which would necessitate 30 or 40 volts at least, without causing a tremendous adverse effect on the patient. I do not think that thiopental would be sufficient to anesthetize the patient against that dose. I wish you would say something about the cats you studied, Dr. Stevenson.

DR. LEWIS D. STEVENSON: I can only say that I studied their brains and found extensive changes in the Purkinje cells. This is the first intimation I have had of what happened to those cats.

Leukemia with a Clinical Syndrome Simulating Poliomyelitis. DR. E. D. FRIEDMAN.

CASE 1.—A. M., a boy aged 3 yr., began to limp late in September, 1941, the child stating, "My foot gets tired." Roentgenographic examination of the bones of the lower extremities revealed no abnormality. The blood cell count was within normal limits. Orthopedic examination was noncontributory. The difficulty in walking grew steadily worse. The patient later exhibited increased weakness, pallor, and low-grade fever. The neurological status was normal except for diminished patellar reflexes. Later examination of the blood and the bone marrow revealed the signs of acute myeloblastic leukemia. The spleen and liver became enlarged; there was occasional bleeding from the gums; ecchymoses appeared over the right side of the neck and over the sternum. There was no adenopathy. The patient died Nov. 25, 1941.

CASE 2.—B. G., a girl aged 4 yr., in January, 1946, had difficulty in walking because her feet hurt. She refused to walk except under pressure. Orthopedic examination, roentgenographic studies, and general medical examination revealed no abnormalities. Because of a neurosis in the mother, the patient's symptom complex was considered psychogenic. In June, 1946, the patient fractured her left ankle. Examinations on June 24 and July 2, 1946, revealed no evidence of a blood dyscrasia. The neurological status was normal except for diminution of the left patellar reflex. Electrical tests revealed no evidence of a lower-motor-neuron lesion. The patient showed no improvement in the use of the lower limbs, and in August she was hospitalized. She then presented moderate lymphadenopathy and extreme pallor. Examination of the blood revealed the signs of lymphatic leukemia, and studies of the bone marrow confirmed this diagnosis. The liver and spleen were not palpable. Roentgenologic examination of the chest revealed a normal condition. Roentgenograms of the bones showed osteoporosis in the tibias and fibulas and signs of an old fracture at the distal end of the left tibia.

Later, there were widespread adenopathy and enlargement of the liver and spleen. Purpuric spots appeared on the right cheek, below the left eyelid, and on the chest. There was also a brief episode of gross hematuria. The patient had a high fever and died on March 19, 1947.

Comment.—In the differential diagnosis of poliomyelitis, one must consider bone disease, including rickets, syphilitic osteochrondritis, osteomyelitis, epiphysitis, and scurvy with periosteal bleeding. These two cases are the first in my experience in which leukemia appeared in the guise of poliomyelitis—in the second case long before the blood picture became manifest. It is quite likely that the bone lesions of leukemia were responsible for the sensitivity of the lower limbs of these children and the patients' refusal to bear weight on them.

DISCUSSION

DR. NATHAN ROSENTHAL (by invitation): It is fortunate that Dr. Friedman saw these two patients first; otherwise, there might not have been a presentation of poliomyelitis in relation to leukemia. I do not believe I had ever seen the combination of the two before, but since Dr. Friedman called our attention to this peculiar syndrome I have seen a few other cases.

Thrombosis of the Basilar Artery. DR. SIDNEY W. GROSS and (by invitation) DR. JAMES R. LISA and DR. LOUIS J. SOFFER.

Occlusion of the basilar artery is rarely diagnosed before death, and it is an unusual finding post mortem. Nevertheless, the clinical syndrome of basilar-artery occlusion is fairly characteristic, and it should be possible in many cases to make a correct clinical diagnosis.

During the past year two cases of occlusion of the basilar artery came under our observation. In the first case the clinical picture was rather typical. The patient, a white man aged 60, died at home, and no necropsy was done. He had had hypertension for about 10 yr. but was without symptoms. In May, 1949, he began to complain of numbness of the right hand. This did not disturb him greatly, and he continued to work. About six weeks before his death there developed "thick speech" and weakness of one side of the face. He remained at home in bed for several days. He seemed to improve and was up and about until the evening when I first saw him. About 7 p. m. he suddenly complained of feeling dizzy and lightheaded. He was seen

by his family physician, who found him to be alert but unable to talk. Within an hour he became unconscious, and irregular respiration of the Cheyne-Stokes type developed. I saw him about three hours later. He was unconscious but not cyanotic. The pulse rate was 108 a minute; the temperature was 100.8 F. The pupils were small and did not react to light. The reflexes were all hyperactive, those on the right being greater than those on the left. The Babinski sign was strongly positive on each side. Painful stimulation evoked tonic spasms of the decerebrate type in all extremities. The temperature rose rapidly, and he died about 10 hr. later.

In our second case, a white man aged 61, seemed always to have been in good health. There was no history of hypertension or diabetes. On June 2, 1949, he suddenly became confused and had difficulty in walking. This lasted only a few minutes and then cleared up, and he seemed well until June 9, when he suddenly arose from his chair and tried to talk to his son. He mumbled a few words, frothed at the mouth, and fell to the floor. His right arm became spastic, and he lost consciousness. He was seen by a physician, when his blood pressure was 110 systolic. After an interval he regained consciousness. He was confused, and his gait was slow and unsteady. After a few hours he again became unconscious, and he was admitted to the hospital late that night. On admission the patient was in coma and was slightly cyanotic. The pulse rate was 70 and the blood pressure 150/90. The temperature was 99 F. All the extremities were spastic. The head was turned to the left. The tendon reflexes were hyperactive, with bilateral ankle clonus. The plantar responses were normal. The general physical examination disclosed no abnormalities. The cerebrospinal fluid was clear and colorless and under a pressure of 120 mm. There were 7 red blood cells per cubic millimeter. The total-protein content was 23 mg. per 100 cc. of fluid. During the night and early morning the patient had convulsive seizures lasting two minutes and recurring about every half-hour. His temperature rose to 107 F. The next morning he was in profound coma. All the reflexes were absent. The pupils were small and nonreacting, and the blood pressure was 100/70. A consultant suspected a frontal neoplasm. Bilateral frontal trephination and ventricular puncture did not disclose any abnormalities. The patient died at 4 p. m. on June 10, about 20 hr. after admission to the hospital.

Autopsy was limited to examination of the brain, which had retained its shape. The left vertebral and the basilar arteries were 4 mm. in diameter, appeared tense, were distended with recent thrombus, and had many atheromatous patches. The right vertebral artery barely averaged 1 mm. in diameter and had a very soft, thin wall; its lumen was patent. The thrombus distended the basilar artery through its entire length up to the superior cerebellar branch and extended into several small pontile branches and the anterior inferior cerebellar branch. The posterior cerebral artery and the posterior communicating branches were collapsible and had patent lumens. The internal carotid artery and the middle and anterior cerebral branches were normal. The circle of Willis was completed by a small anterior communicating artery.

The pons, medulla, inferior and superior colliculi, midbrain, and cerebellar vermis were soft and putty-like and disintegrated on gentle handling. The cervical portion of the cord was normal.

Histologic section of the basilar artery revealed intense atherosclerosis. The lumen was occluded by a mixture of atheromatous material and fresh blood. Recent hemorrhage was present in the outer parts of the cholesterol deposits, which were becoming organized by granulation tissue. The muscular walls were thin and partially fibrosed. The adventitia had a large lymphocytic and plasmocytic infiltrate.

The diagnosis was cerebral atherosclerosis, and recent thrombosis of the basilar artery, with malacia of the cerebrum, pons, medulla, and cerebellum.

DISCUSSION

DR. SAMUEL BROCK: Thrombosis of the basilar artery or some of its branches occurs more frequently than is generally recognized. I am glad that the authors called our attention to the excellent article by Kubik and Adams (*Brain* **69**:73, 1946), in which they reported 17 fatal and seven nonfatal cases.

The authors have touched on the clinical attributes of this syndrome. The onset is usually sudden; there are brain-stem phenomena with confusion, and even coma. There may be premonitory signs and symptoms referable to the brain stem, which are not of great diagnostic value. What gives the syndrome away are the cranial-nerve signs, especially the oculomotor; facial

paralysis and other cranial-nerve signs may appear. There is usually a bilateral Babinski toe sign. Moreover, there is paresis or paralysis of three or four limbs with spasticity; decerebrate phenomena are not uncommon. In a recent unproved case, seen about six weeks ago, the patient, a man aged 80 with long-standing hypertension, suddenly became confused and dizzy; he vomited and became drowsy. There was some headache. Examination revealed a bilateral Babinski toe sign, a tendency toward recurrent spasms in the lower limbs, as well as in the upper, and then decerebrate-rigidity phenomena, including partial Magnus-de Kleijn reflexes. Oculomotor paralyses were noted. The spinal fluid showed mild evidence of subarachnoid hemorrhage. Death supervened two weeks after onset of symptoms.

DR. LEWIS D. STEVENSON: What interests me most in this condition is the fact that these patients clinically manifest movements in the extremities that are often mistaken for convulsions. Dr. Kennedy has had a good deal of experience with these phenomena in cases of this kind and in other cases; I should be happy if he would discuss this problem of basilar thrombosis, particularly with reference to the convulsive-like movements seen in these patients and the differentiation of lesions of the basilar artery and cortical lesions in these cases. Dr. Gross pointed out that in one of the cases the physician thought the patient had a frontal-lobe tumor because he had convulsions. He did not describe the convulsions, but perhaps he will say more about them in his closing comments.

DR. FOSTER KENNEDY: I have seen two types of movements. One is the decerebrate position with extensive convex movements of the whole body; the other consists in automatic ambulatory movements, the walking movement often being rather slow. These movements are not at all like the movements of a cortical lesion, any more than the extensor plantar reflex is like a cortical condition. The legs are not paralyzed of course, but have an automatic walking movement. Dr. Brock has spoken of the bilaterality of the Babinski toe reflex; the automatic movement is bilateral, as is the extensor reflex, because the lesion is on both sides. Thrombosis of the basilar artery is characterized by confusion, evidence of cerebral anemia, dizziness, and often quadrilateral difficulties with peculiar movements, such as Dr. Stevenson has spoken of. Dr. Stevenson took care of one of the most distinguished of our colleagues, who, under Dr. Stevenson's competent surveillance, survived, and I knew him with happiness for many years after he had had a partial basilar thrombosis.

DR. E. D. FRIEDMAN: I have seen a few of these cases, as have most of us who have access to much clinical material. The first case I saw was demonstrated by Oppenheim; the patient exhibited oculomotor paralyses; these were ascribed to occlusion of the basilar artery with ischemia of the upper twigs of the basilar artery, which supply part of the midbrain; at this level these vessels anastomose with some of the branches of the posterior cerebral artery. If to these oculomotor paralyses are added small, fixed pupils and bilaterality of signs with brain-stem phenomena in the patients who survive, one may be fairly certain that the lesion is a thrombosis of the basilar artery. I believe you have a brain specimen, Dr. Stevenson, which you acquired recently in a case in which I ventured the diagnosis of basilar-artery occlusion with softening of the pons.

DR. LEWIS D. STEVENSON: At Bellevue we have had a number of cases of occlusion of the basilar artery. The part of the pons that is always affected is the base, including the corticospinal tract and also the afferent pyramidal tract, which has to do with the lateral conjugate movements of the eyes, which are sometimes paralyzed. Seldom is the tegmentum involved in the softening, and therefore there are rarely any sensory phenomena; but the subject is one which requires more careful analysis of material than we are now in possession of. I should like Dr. Gross to tell us more about these convulsions. He calls them convulsions, not decerebrate movements or quadriplegic movements, but convulsions.

DR. SIDNEY W. GROSS: Textbooks on neurology mention thrombosis of the basilar artery briefly or not at all. Oppenheim gives a fairly good description of the syndrome. In a series of 100 cases of cerebral thrombosis (Foix and Ley, cited by Wilson), not one case of thrombosis of the basilar artery is mentioned. Not only are lesions of the basilar artery of this type overlooked, but aneurysm of the basilar artery is also rarely diagnosed clinically. Of two cases of aneurysm of the basilar artery discovered at autopsy, the clinical diagnosis was subdural hematoma in one and cerebellar tumor in the other.

With regard to the seizures, there can be little doubt that the patient had real convulsions. They were observed by his nurse and by the neurologist who saw him.

Dr. Friedman called attention to the small, nonreacting pupils. This sign was observed in both our patients.

Dr. Stevenson and Dr. Kennedy both pointed out that thrombosis of the basilar artery is not necessarily fatal. Of the patients reported by Kubik and Adams, seven for whom the diagnosis seemed practically certain on clinical grounds survived.

NEW YORK NEUROLOGICAL SOCIETY

Lewis D. Stevenson, M.D., *President, Presiding*

Regular Meeting, May 2, 1950

Metastatic Tumors of the Central Nervous System: Study of Two Hundred Six Cases Confirmed at Autopsy. Dr. Stanley Lesse (by invitation).

This study was based on a series of 1,700 consecutive autopsies performed on patients who died of cancer at the Montefiore Hospital for Chronic Diseases, in 595 of which the central nervous system was examined. Metastases to the central nervous system were noted in 206 instances, this figure representing 34.6% of the 595 cases in which the brain and spinal cord were examined and 12.1% of the unselected series of 1,700 autopsies. The following structures were the commonest sources of metastasis: breast, 71 cases, with involvement of the central nervous system; lung, 50 cases, with malignant lymphomas in 13; kidney, 10 cases, with leukemias in 7 cases; thyroid, 6 cases, with multiple myeloma in 5 cases; prostate, 5 cases; colon, 4 cases; nasopharynx, 4 cases, and stomach, 4 cases. Of the 206 patients with lesions of the central nervous system, 123 were women and 83 men, the discrepancy in the figures being accounted for by the fact that 71 patients had primary lesions in the breast. The mean age of onset of the primary lesions was in the early forties in the women and in the late forties in the men. Of the 206 patients, 128 had symptoms and in 106 of these the diagnosis was made accurately. In only 9 patients were the metastases to the central nervous system the only metastatic lesions in the body (local involvement of lymph nodes excluded). The meninges alone were involved in 85 cases; the brain and meninges, in 42 instances and the brain alone, in 79 cases. A single metastatic focus was noted in 37 brains, and multiple lesions, in 84 brains. Headaches, mental and personality changes, and evidences of motor dysfunction were the commonest signs and symptoms.

DISCUSSION

Dr. Harry M. Zimmerman: Dr. Lesse indicted a startling discrepancy between the incidence of tumor metastases to the brain in his series and the statistics available in published reports of metastatic tumors to the central nervous system. He suggested that one of the factors in this discrepancy is the number of long-term cancer patients in the terminal stages of the disease at the hospital from which he gleaned these statistics. There is another, and perhaps more important, reason that the incidence of metastatic tumors of the central nervous system was so high in this series. The hospital specializes in admitting patients with advanced carcinoma of the lung and patients with cancer of the breast, and both these types of cancer have a notoriously high incidence of metastasis to the nervous system. Montefiore Hospital has relatively few patients with biliary-tract carcinoma, from which metastases to the nervous system are less frequent, and fewer with cancer of the lower part of the gastrointestinal tract.

Dr. Lesse's point that cancer of the breast in his series was far more important as a source of metastasis to the brain than cancer of the lung is explained, I believe, by the fact that many of the patients with breast cancer had, in reality, metastases to the dura; in a sense, it is not fair to include dural metastases in a series in which the brain and spinal cord are said to be the seat of the metastatic lesions. If the dural metastases are eliminated, the incidence of breast cancer with secondary lesions in the nervous system as compared with that of pulmonary cancer with such metastases would be in keeping with the findings of other authors, that is, that cancer of the lung is more important as the primary site of metastases to the central nervous system.

Dr. Peter G. Denker: I should like to stress a clinical point, that is, the difficulty of differentiating a primary lesion of the brain at the onset and a possibly metastatic one. At Bellevue Hospital, where one sees many cases of cerebral metastases from carcinoma of the breast

or lung, the general state of cachexia of the patient has been found helpful in differentiating a primary and a metastatic tumor. Though the clinical picture may be the same in the two conditions, a far greater percentage of patients with metastatic tumor are cachectic, and the presence of cachexia may be the first clue that the intracranial lesion is metastatic rather than primary. Likewise, in my experience, papilledema is far less common with metastatic than with primary neoplasms of the brain.

Dr. Henry Alsop Riley: I agree with Dr. Zimmerman that metastases to the dura and the soft meninges should be differentiated from the metastases actually developing within the cerebral substance. In a discussion of metastatic disease of the central nervous system, one certainly cannot include metastases to the coverings. It would be of interest to know the number of tumors which metastasize into and develop in the cerebral, cerebellar, or brain-stem substance and the spinal cord, as compared with the number which affect these structures by pressure from without.

Did the majority of these patients die because of their primary disease? How many of them died from the results of the metastases to the central nervous system?

Although it was stated at a recent conference at the Neurological Institute that the surgeons are willing to operate on known metastatic nodules when they think the lesion is single, it has been my experience in the ward service that if a primary tumor was shown to exist in any other system of the body, in conjunction with what seemed to be a metastasis to the central nervous system, the surgeon was usually loath to attack the metastatic lesion. I believe that in a number of instances in which the metastatic nodules have been removed from the central nervous system, under the impression that the neoplasm was an intrinsic neural tumor, a rather large number of patients have lived for a considerable length of time and this prolongation of life at least has been of some comfort to their families. If the primary focus had been demonstrated prior to operation, I doubt whether the surgeon would have operated. I feel that in every instance in which other metastases are not present the patient should be given the benefit of the doubt and the demonstrated cerebral neoplasm should be removed.

Dr. Stanley Lesse: Dr. Zimmerman is correct as to the frequency of meningeal involvement in cases of breast carcinoma. Of the 71 cases of breast cancer with metastases to the central nervous system, including the meninges, metastasis to the meninges alone occurred in 33, and in only 8 cases of carcinoma metastatic from the lung were the meninges involved alone; so the lung is probably the commonest source, a finding which corroborates the observations in other series.

Whether the lesions of the central nervous system or the general metastases were the cause of death, Dr. Zimmerman can perhaps answer better than I. I might say, however, that in most of the cases in which autopsy was performed the patient was cachectic and showed multiple lesions throughout the viscera. I would assume that most of the patients died from their general metastases, rather than from the cerebral lesions.

Dr. Harry M. Zimmerman: I regret I cannot give the exact figures, but I should say that a relatively small percentage of patients died from the cerebral metastases—I should guess, about 5%.

Dr. Stanley Lesse: Cachexia is more frequent in patients with primary neoplasms in the general viscera with metastases to the central nervous system than in patients who have primary lesions in the nervous system, as noted frequently in hospitals like Bellevue or Montefiore. However, in looking over some of the records at the Neurological Institute, I noted that a number of patients appeared with no signs or symptoms relative to the primary neoplasm and that the first abnormal signs which brought them to the hospital were signs or symptoms referable to the central nervous system. Many were well nourished. However, in general, the point is well taken.

Analysis of Choreoid Hyperkinesia in Primates. Dr. Malcolm B. Carpenter (by invitation).

By stereotaxic technique, electrolytic lesions were placed in the subthalamus of 46 rhesus monkeys. In 40 of these animals lesions involved the subthalamic nuclei of one or both sides. Choreoid hyperkinesia was observed in 31 animals, and of these, 10 exhibited unequivocal

choreoid hyperkinesia appropriate for analysis. The purposes of analysis were to determine (*a*) the neural mechanism necessary for the maintenance of choreoid hyperkinesia, and (*b*) a procedure which would eliminate this dyskinesia without producing paresis or other motor deficit. Nine animals were subjected to 16 surgical analyses, and three animals were subjected to pharmacological analysis.

Choreoid hyperkinesia was eliminated or reduced in violence and persistence unilaterally by destruction of appropriate volumes (varying from approximately 7 to 17%) of the internal segment of the globus pallidus contralateral to the side of the symptom. Neither autonomic disturbances nor easily detectable motor deficits resulted, and survival was not jeopardized.

Bilateral destruction of appropriate volumes of the globus pallidus or of the lenticular fasciculus ameliorated the severity of the dyskinesia but produced autonomic disturbances and motor deficits.

Intravenous injection of mephenesin (myanesin®) in doses which were not hypnotic did not influence the abnormal activity.

The hypothesis was presented that integrity of the pallidum is necessary for the maintenance of the neural mechanism responsible for choreoid hyperkinesia resulting from lesions in the subthalamic nuclei.

Arnold-Chiari Malformation: Report of a Case. Dr. William H. Bloom (by invitation).

A woman aged 32 was admitted with the history of progressive difficulty in gait and paresthesias in all extremities for one year. She also complained of diminished "sense of touch," blurring of vision, and diplopia, made worse by sudden movements of the head, and suboccipital pain, which radiated to both shoulders on sneezing. Examination disclosed a poorly developed woman, 4 ft. 5 in. (135 cm.) tall and weighing 78 lb. (35.4 kg.), with pronounced kyphoscoliosis. She presented numerous stigmas of degeneration, such as high-arched palate, clubbing deformities of several fingers, vascular nevi, and many café-au-lait spots. The gait was ataxic, with veering to the left. The corneal reflexes were depressed, and fibrillary twitchings of the tongue were seen. Horizontal nystagmus was noted in both directions of lateral gaze. Fairly pronounced bilateral signs of pyramidal-tract involvement and mild bilateral cerebellar signs were found. Lumbar puncture revealed partial block on jugular compression and a protein content of 79 mg. per 100 cc. Roentgenograms of the skull showed mildly increased convolutional markings and platybasia. A myelogram showed the typical changes of the Arnold-Chiari deformity in the region of the foramen magnum. Suboccipital craniectomy and high cervical laminectomy verified the preoperative myelographic diagnosis. No attempt was made to excise the cerebellar tonsils or to free the adhesions about them. The dura was left open for decompression.

The traction theory of the Arnold-Chiari malformation was discussed, and the extreme scoliosis in this case was offered as a possible basis for spinal-cord fixation. The myelographic findings were shown, and their importance in the preoperative diagnosis was emphasized, only three other cases of preoperative myelographic diagnoses having been reported in the literature. The necessity of surgical decompression without interference with the displaced cerebellar tonsils was mentioned in the treatment of the adult with the Arnold-Chiari malformation.

DISCUSSION

Dr. Lewis D. Stevenson: This case is a somewhat unusual example of the syndrome.

Dr. Leonard I. Malis: This case is one of three that have been seen at Mount Sinai Hospital in the past three years which have been very much alike in their symptoms and in the method of proving the diagnosis. The first was presented at the neurosurgical meeting at the New York Academy of Medicine two and one-half years ago; the patient had a myelogram almost identical with the one presented here and was clinically very much like this patient, except that the only clinical finding which led us to suspect the Arnold-Chiari syndrome before operation was the presence of a tuft of hair on the lower thoracic portion of the spine. This led to roentgenologic examination and the myelographic demonstration of the Arnold-Chiari syndrome. The condition was treated surgically in the manner described by Dr. Bloom. In another, more recent case myelographic proof of a very small tonsillar herniation was also obtained. This patient had definite platybasia but was not thought actually to have an Arnold-Chiari malformation; rather, it was believed that the protrusion of the cerebellum was due to the platybasia; I shall show

what was demonstrated at the operation. The first slide is of the patient seen two and one-half years ago. The condition resembles that described by Dr. Bloom except that the tonsils did not overlap; they extended all the way down to the third cervical level. In the slide of the patient's recent appearance there is much less tonsillar protrusion, the tonsils extending only to the lower edge of the atlas. We have taken a slightly oblique photograph to demonstrate the direction of the first cervical root, and it is not turning cephalad, as it would be expected to turn in the true Arnold-Chiari malformation. However, the treatment was the same. In this case the diagnosis had always been multiple sclerosis, through many years of observation, and the finding in the myelogram of this partial protrusion suggested that operation might relieve the patient. All three patients have done well, and all have had considerable improvement in their neurological status.

One other point ought to be made. Until Gardiner's presentation a year ago at the annual meeting of the American Neurological Association, there were only 18 cases of surgical treatment of the Arnold-Chiari syndrome in the literature, and in only two or three of these had the patient survived. Gardiner presented a series in which 16 patients had recovered after operation, so that he had had good results in more than the total number of cases in the literature. In none of his cases was cerebellar tissue resected or the adhesions freed. He does not believe that traction mechanism is present in cases of this malformation; he believes that the condition is due purely to chronic hydrocephalus. Yet he did not free the adhesions, and he obtained good results.

Dr. E. Jefferson Browder: I have had three adults with the Arnold-Chiari syndrome and, of course, quite a number of children. I do not recall having heard of a patient with a pronounced scoliosis and the Arnold-Chiari syndrome. At least I have never seen such a case, and if one has been reported I do not recall having read about it. Perhaps one could postulate that the scoliosis had created lengthening of the cord or traction on this structure. I have had four patients with scoliosis which produced paraplegia, and I am sure all neurosurgeons have seen patients in whom scoliosis has resulted in paraplegia, and scoliosis of no greater degree than that described in this case. I wonder whether such a curve in the vertebral column is sufficient to produce traction on the cord over a long period and to result in this downward movement of the hindbrain and cerebellum.

Dr. H. A. Riley: Did I understand Dr. Bloom to say that no cases of the Arnold-Chiari syndrome had been investigated pathologically?

Dr. William Bloom: In answer to Dr. Riley's question: In no cases were there postmortem findings that would rule out fixation of the spinal cord in cases of the Arnold-Chiari malformation. Autopsy has been done in many cases, but in most of them it has been confined to the area of the deformity. The only way to prove that there is no fixation of the cord would be to do a careful dissection of the spinal cord within the spinal canal, and that has not been done. Any proponents of the theories of the cause of the Arnold-Chiari malformation that do not agree with the traction theory would presumably have to rule out fixation of the spinal cord in order to present any convincing proof against that theory.

In reply to Dr. Browder's question about the curvature in the vertebral column producing traction: I do not know, and I cannot think of any way of actually proving it other than at necropsy.

This case represents one of three cases of the Arnold-Chiari malformations diagnosed preoperatively by myelography which Dr. Malis will publish.

Dr. H. A. Riley: Has the caudalmost extent of the spinal cord not been determined in these pathologically investigated cases?

Dr. William H. Bloom: Apparently not; it is remarkable that such studies have not been done; in fact, adequate roentgenographic studies of the spinal column were often not made in cases which were published as instances of the Arnold-Chiari malformation without associated spinal deformity.

Dr. Lewis A. Stevenson: I think some have been done, but perhaps have not been published, Dr. Bloom. I know that I have one or two of my own that should be published.

Dr. Leonard I. Malis: I believe that what Dr. Bloom stated is that there is no pathological proof in any case of Arnold-Chiari malformation without fixation of the cord. A few cases have been reported in which no evidence could be obtained of fixation of the cord, but none of these

cases have yet had pathological study. Of course, many careful pathological studies of cases of cord fixation have been demonstrated, from the original papers of Arnold and Chiari, on through the years.

Subdural Hematoma Developing During Hospitalization. Dr. Martin Green (by invitation) and Dr. Max Fink (by invitation).

A 58-yr.-old white woman, a nurse, was admitted to Bellevue Psychiatric Hospital because of a five-year history of mental and personality changes. The following neurological signs were present: (1) an organic mental syndrome with elements of aphasia, apraxia, and disturbances in body scheme; (2) a left homonymous visual-field defect; (3) left hemisensory defect in pinprick and touch sensibility. A pneumoencephalogram revealed generalized dilatation of the ventricular system without displacement or distortion. The cortical markings were increased bilaterally. The patient was kept in the hospital for further study, and during this period bruises were noted over her head and face. These were thought to be sustained from falls or from bumping into objects in the ward. Three months after admission the patient gradually became stuporous, exhibited myoclonic movements, and suffered left hemiparesis. Bilateral trephination disclosed a huge subdural hematoma on the right side and a small subdural hygroma on the left side. A biopsy specimen was taken from the left parietal lobe. Microscopic examination of the tissue showed numerous senile plaques and Alzheimer cells, compatible with the diagnosis of Alzheimer's disease.

The signs of progressive disease of the cerebral hemispheres which this patient exhibited during the latter part of hospitalization were initially interpreted as the end-stage of an organic psychosis. Trephination was done to exclude subdural hematoma, although this diagnosis was considered improbable.

Patients with organic psychosis in mental-disease hospitals are particularly liable to head trauma, which may initiate subdural hematoma. This case illustrates the fact that progressive neurological signs in such patients should be evaluated with this consideration in mind.

DISCUSSION

Dr. Lewis D. Stevenson: This case is interesting from many angles, including the fact that the diagnosis of presenile dementia was made by biopsy. The histologic study showed presenile dementia. I was surprised to see how many of these cases are accurately diagnosed, and accurately diagnosed only by this newer method of biopsy that is now in use at Bellevue. It seems to me that some discussion would be worth while as to the possibility of making a diagnosis of presenile dementia clinically rather than to say that the patient has an organic type of psychosis.

Dr. Martin Green: So far, cerebral biopsies were made in 25 cases. These are not all cases of presenile or senile degenerative disease. Some biopsy specimens were taken as controls at the time of trephination for subdural hematoma. We have not analyzed the cases clinically, but in general there is a great variation within the group. There does not seem to be a typical clinical syndrome.

Of the 25 cases, biopsy showed histologic changes compatible with the diagnosis of Alzheimer's disease in seven. Most pathologists feel that age is the factor that determines whether a case should be called one of presenile or of senile degenerative disease. Some of these patients were 50 yr. old or more, and their disease should probably be classified as senile psychosis.

Dr. H. A. Riley: Were these biopsy specimens obtained at the time of operation or by a former trephination for that purpose?

Dr. Martin Green: They were taken at the time of trephination.

Dr. H. A. Riley: The ordinary burr was used? Do you remember, Dr. Stevenson, Purves-Stewart's visit many years ago? He told me he had a little burr he used to drill a hole in the skull and through this burr hole he could remove a piece of cortex. I never saw him do it.

Dr. Lewis A. Stevenson: I have seen him do it in his clinic at Westminster Hospital, London. He had a moving burr, but he used it to introduce air into the ventricle, so that he would not need the services of a neurosurgeon. (Incidentally, Purves-Stewart was a Scotchman.) I might say that we were able to make a diagnosis of dementia paralytica with these small biopsy specimens. All the features of dementia paralytica which appear under the microscope were

present. We cut this little cylinder of tissue in two, embedded one-half in pyroxylin and froze the other half, and made Nissl and trichrome stains on the embedded tissue and Cajal stains on the frozen section.

DR. H. A. RILEY: How do you get the specimen—through just a small hole?

DR. LEWIS A. STEVENSON: Yes. I think Dr. Echlin has been doing most of the biopsies. The diagnosis of dementia paralytica was easy to make clinically and serologically, but it is notable that from this small specimen one can demonstrate all the histologic changes one expects to find in this disease.

Periarteritis Nodosa with Involvement of the Central Nervous System, Followed by Recovery: Report of a Case. DR. LOUIS J. MICHEELS (by invitation).

In the last 20 yr. it has become apparent that the aspect of periarteritis has changed. In the first place, since the sulfonamides were introduced into medical treatment, in 1936, an increased incidence of the disease has been reported by Rich. Second, greater knowledge of the disease has resulted in an increasing recognition of milder and atypical cases, with recovery or remission of symptoms. Third, in an increasing percentage of cases involvement of the central nervous system has been reported.

A white woman aged 37 was admitted to Bellevue Hospital with a history of migrating arthritis of three-months' duration. She was treated with gold-compound and nonspecific-protein injections. Eighteen days prior to her admission, personality changes, muscular tenderness, unsteadiness of gait, and fever had developed. On examination the patient appeared to be delirious, confabulating and negativistic. A morbilliform rash was present on the trunk and extremities. There were weakness of the left upper extremity, bilateral foot drop, hyperactive deep reflexes, a bilateral Babinski sign, and fine nystagmus on lateral gaze. The blood pressure was 90/60; the pulse rate, 82, and the temperature 101 F. Laboratory data included pronounced leukocytosis and eosinophilia up to 55%. Biopsy of the left deltoid muscle revealed typical lesions of periarteritis nodosa. The spinal fluid, except for a protein content of 87 mg. per 100 cc. on the first lumbar tap, was normal. An electroencephalogram indicated diffuse cerebral dysfunction. Precipitin and skin tests for Trichinella gave positive results.

High, spiking temperatures developed. On the seventh hospital day aureomycin was given. Her temperature returned to normal, and progressive improvement in physical and laboratory findings was noted. Two months after onset of the acute illness the patient was discharged with slight residual paresis of the left upper and the right lower extremity, left hemiamblyopia and a normal blood cell count. She has been followed for two and one-half months and has continued her favorable progress.

Further investigation of a possible relation of anaphylactic type between trichinosis and periarteritis nodosa was suggested.

DISCUSSION

DR. H. A. RILEY: Were there any palpable local or general enlargements of the superficial blood vessels?

DR. LOUIS J. MICHEELS: We did not notice any cutaneous or subcutaneous nodules; apparently the arteries most involved outside the central nervous system were those in the muscles, as demonstrated by severe pain to touch and passive and active movement and by a muscle biopsy.

Multiple Tumors of the Spinal Cord: Report of a Case. DR. HOWARD E. MEDINETS (by invitation).

A salesman aged 38 complained of nuchal pain of seven-months' duration and progressive weakness of the left lower extremity of four-months' duration. Examination showed atrophy of the small muscles of the left hand, slight weakness with hyperactive reflexes of the left lower extremity, and diminished sensation below the fifth cervical dermatome on the right. Roentgenograms of the spine revealed destruction of the left pedicle and the left lateral third of the body of the 11th thoracic vertebra. Myelography with injection of ethyl iodophenylundecylate (pantopaque®) via the lumbar route demonstrated a globular defect at the fourth lumbar level on the left and a globular, totally obstructive defect at the first lumbar segment. Ethyl iodophenylundecylate myelography via the cisterna magna demonstrated a totally obstructive globular

defect at the fifth cervical segment. At the first operation, laminectomy of the fourth to the seventh cervical vertebra was performed. An intradural perineurial fibroblastoma, 2.5 cm. in diameter, arising from the sixth cervical segment was removed. The patient did well until the fourth and fifth postoperative days, when flaccid paraplegia and a sensory level at the first lumbar dermatome bilaterally developed rapidly. As an emergency procedure, laminectomy of the 11th thoracic to the fourth lumbar vertebra was performed. At the fourth lumbar segment a perineurial fibroblastoma, 2.5 by 1.5 by 1.5 cm., was removed. Cephalad to this was an arachnoid sac filled with purple blood which was evacuated. Between the second lumbar and the 12th thoracic segment was a hemorrhagic perineurial fibroblastoma, 5 by 2 by 2 cm., which was removed. At the 11th thoracic segment the fourth perineurial fibroblastoma, 3.5 by 2 by 2 cm., was removed. After the second operation the sensory level receded, and strength gradually returned to the lower extremities. Extensive rehabilitation therapy was given. Six months after the second operation the patient was engaged in active work and showed no significant neurological disability.

This patient had presented four discrete perineurial fibroblastomas of the spinal cord without any other manifestation of Recklinghausen's disease. The case illustrated the gratifying results that can be obtained in the treatment of most tumors of the cord if the diagnosis is made early —before irreversible changes develop in the cord. Myelography is the key to the early diagnosis of such tumors. In the case presented, in spite of the severe exacerbation of symptoms due to hemorrhage into a second tumor following operation on the first tumor, prompt treatment resulted in recovery.

DISCUSSION

Dr. Leo M. Davidoff: We were fortunate in this case that the tumor at the 11th thoracic segment, which could not be reached by ethyl iodophenylundecylate either from the lumbar or from the cervical injection, manifested itself in the plane roentgenogram by atrophy of the vertebral body. The contrast medium, therefore, gave us information as to the existence of the cervical tumor and the lumbar tumors, and we knew from the roentgenogram about the tumor at the 11th thoracic segment, so that we extended our laminectomy far enough to include that region and found the tumor there.

Dr. Medinets has pointed out that prompt treatment of the paraplegia following the first operation was an important item, and I believe that is so. We all know from the experience with extradural abscesses that if the abscess produces a paraplegic state and this is neglected for two or three days, even though the abscess may be drained and the patient recover from the infection, the paraplegia is likely to persist. There are few cases on record in which the patient recovers if a period of paraplegia is allowed to remain more than three days.

The failure of these large tumors to produce more pronounced neurological signs in this case is difficult for me to understand, and I hope some of you will comment on that. The tumors, while they may not have been present very long, were there long enough to produce atrophy of the bone, and that means six months or more; why he had no more than mild pyramidal tract signs and hemilateral sensory changes I cannot understand.

Dr. Lewis A. Stevenson: It seems to me that in the roentgenogram of the thoracic portion of the spine two of the lower bodies were close together. Were they fused, by any chance, as one sometimes sees in Recklinghausen's disease?

Dr. Howard E. Medinets: In the lateral view there was some narrowing of the interspaces, but they were not fused.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

D. Denny-Brown, M.D., *Presiding*

Regular Meeting, Oct. 11, 1950

Relation of Order of Maturation of Nuclei and Tracts to Degenerations of the Central Nervous System. Dr. J. Godwin Greenfield.

The date of maturation, i. e., the appearance of Nissl granules in the perikaryon and of myelin around the axon, has at least as much relation to disease and degeneration of nuclei and tracts

in the central nervous system as has phylogenetic age; it is also much more easily studied and more definite, since we know little about the genealogical tree of Homo sapiens. This important approach to neuropathology has been neglected during the last 50 yr.

In the spinal cord, tabes affects first Flechsig's middle root zone, whereas in hereditary perforating ulcer of the foot the dorsal root zone degenerates first. In olivopontocerebellar degeneration it is more correct to relate the disease to Essick's cell bands than to the neocerebellum and its related nuclei in the pons and medulla. Degeneration commences in late-maturing systems also in Huntington's (chronic progressive) chorea and Alzheimer's disease (presenile sclerosis).

Many diseases which appear at birth or in early infancy may also be related to the state of maturity of the cerebrum at the time of their onset. This is seen in état marbré, if Norman's theory of its causation by thrombosis of the veins of Galen (venae cerebri internae) at birth is correct, and also in kernicterus, which affects only nerve cells which have reached a certain degree of maturity at birth. A similar relationship can be seen in many forms of maldevelopment of the brain, e. g., lissencephalia and ulegyria. It is very evident in the "late infantile metachromatic leukodystrophy," described by Greenfield in 1933, in which the myelin laid down after birth suffers first.

DISCUSSION

DR. STANLEY COBB, after discussing the general difficulty in defining maturity, asked whether there was any direct evidence that oligodendroglia lays down myelin, and whether *pathoklise*, in the sense of Vogt, could be considered in relation to the disorders discussed.

DR. CHARLES KUBIK reported a case of metachromatic encephalopathy which he had encountered. The disease begins at the age of about 6 yr., and death in this case occurred at the age of 12 yr.

DR. PAUL I. YAKOVLEV stated that status marmoratus presented lesions varying from hypermyelination to necrotic softening. He asked whether it could not be that anoxia at birth stimulates increased activity in the oligodendroglia at a time when this tissue deposits myelin. He also expressed the belief that the basic architectonic patterns, namely, the reticulate, the nucleated, and the laminated, could each be specifically liable to disease, with resulting distinctive pathological characteristics. In kernicterus nucleated patterns are evident; in Pick's disease, laminated patterns, and in nutritional deficiencies and encephalitis, the reticulate pattern.

DR. CLEMENS E. BENDA agreed that status marmoratus is not a prenatal development anomaly.

DR. RAYMOND D. ADAMS, DR. BRONSON CROTHERS, and DR. LEO ALEXANDER also spoke.

DR. J. GODWIN GREENFIELD: I have been gratified that I have not had more adverse criticism of my suggested approach to neuropathology. I should have mentioned *pathoklise*, since that concept is closely associated with the idea of the relation of disease to phylogenesis or ontogenesis, of which I have spoken. For example, there may be a chemical difference between systems, related, on one side, to their developmental age and, on the other, to their metabolic requirements. I do not propose to define degeneration, for I think that many metabolic factors, as to the nature of which we so far can only guess, are concerned in degeneration. Among these are enzyme activities, which form a new and fascinating chapter in neuropathology.

Dr. Cobb asked my opinion about the relation of the oligodendroglia to myelin. I think that del Río Hortega made a good case for the synthesis of myelin by oligodendroglia. The evidence of work with "tagged" elements on the lipids in the brain during the first weeks of life goes to show that lipids accumulate in the brain before myelin is formed, probably in some form not stainable by ordinary myelin methods. Myelin is not formed outside the nervous system and transported ready-made, but it is synthesized in situ. The relationship of oligodendroglia to myelin in ontogenesis is also very close.

I do not consider that from the point of view of pathogenesis there is any close relation between tabes and syphilitic optic atrophy. Both the latter and syphilitic lesions of the auditory nerve, in the cases I have examined, are related to meningeal inflammation, but this is not the cause of tabetic degeneration, the pathogenesis of which I do not understand.

Dr. Kubik's case is interesting. There have been other cases of metachromatic leukoencephalopathy of familial type. Norman published such a pedigree, and it was from him that I got the idea of looking for metachromatic lipid in the kidneys and liver. I should not put these cases

into exactly the same group as mine, but without further evidence it is impossible to be dogmatic on this point. That which has struck me is the remarkable similarity of my six cases to one another. Even the ages at death, as well as the histological pictures, have been almost identical. The question whether oligodendroglia degenerates first because it is a more susceptible element is a difficult one. This susceptibility would not, however, explain its degeneration before there is any demyelination, except on an ontogenetic basis. Either something has gone wrong with its development, or something wrong in the development of myelin has interfered with its metabolism. Which is primary I do not know, but they go hand-in-hand.

In reply to Dr. Yakovlev's question: I do not know how much evidence there is that Pick's disease follows a developmental or late-maturing pattern, because we do not yet know what area of cortex matures last. In Alzheimer's disease a good study by Mutrux (*Monatsschr. Psychiat. u. Neurol.* **113**:100, 1947) has shown clearly that senile plaques and Alzheimer nerve cells appear primarily in association areas which mature late, and only in late and severe cases of the disease do we find changes in the projection areas, which mature early. Other diseases, which I have not mentioned, may also be explained on the same basis when more is known about the stages of maturation. For example, in paralysis agitans (Parkinson's disease) the degeneration of certain areas in the substantia nigra may be similarly explained.

I am interested in the support which Dr. Yakovlev and Dr. Benda have given to Norman's view that status marmoratus is not an error of prenatal development, but may be due to birth injury. Perhaps we do not differ much in our interpretation of the hyperplasia which affects the remaining myelin in that condition. My concept is that of a hyperplasia of replacement, similar to the hyperplasia of one kidney when its fellow is damaged early in life. I am not quite clear about Dr. Yakovlev's comment on kernicterus. My point was that whatever happens to the nerve cells that stain yellow is probably related to their need for oxygenation and metabolic exchange, which must be much greater in cells which are maturing and forming myelin than in those which are still in the neuroblast form, at the time of birth.

I think I have answered Dr. Benda's question about degeneration and metabolism. That question has been assuming importance for many years and will continue to do so until we understand more clearly why these various diseases are progressive. For example, a nerve cell may go on degenerating after mechanical damage, sometimes rather slowly. This degeneration may be due to alterations in the enzyme systems arising from simple mechanical damage.

As regards the differentiation of the forms of diffuse cerebral sclerosis, I did not attempt to open that large and difficult question. I have recently published a paper on certain views which I hold on the pathogenetic classification, especially in relation to the Danish monographs by Einarson and Neel. I do not consider that because there is diffuse demyelination in the brain, together with overgrowth of neuroglia, the disease is therefore any entity. There are so many causes of demyelination, all more or less associated with sclerosis, that it should be considered a (pathological) symptom. Schilder's disease is no more a disease than is paraplegia, and pathology should attempt to differentiate the various forms until their etiology is established.

Dr. Crothers asked an interesting question about the use of the term "congenital." I used it, I am afraid, as meaning something which occurred with birth, the meaning given in the "Oxford English Dictionary." But that is confusing, because the term has been related to development up to birth, rather than to something that happens as a result of birth trauma.

As to Dr. Alexander's question, I have found no alteration in the adrenal cortex in any case of diffuse sclerosis of the brain.

D. Denny-Brown, M.D., *Presiding*

Regular Meeting, Nov. 16, 1950

Problem of Evaluation of Psychotherapy: A Follow-Up Study of Sixty-Two Cases of Anxiety Neurosis. Dr. Henry H. W. Miles, Miss Edna L. Barrabee, and Dr. Jacob E. Finesinger.

The evaluation of psychotherapy was discussed, with a critical review of reported follow-up studies. The results of these studies have not been comparable, partly because of lack of detailed clinical data and precisely defined criteria.

A follow-up study was made on 62 patients with anxiety neuroses two to 12 yr. after intramural psychotherapy.

On the basis of explicit criteria, 23% of the group were found to be greatly improved; 35% were definitely better, and the condition of 42% was considered essentially unchanged. There was a close correlation between the authors' evaluations and the patients' self-estimates.

Analysis of the anamnestic material suggested that a number of factors were related to the course of the illness. Among these were the patient's intelligence, his early home situation, his early neurotic traits, the severity of the clinical symptoms, and his capacity for achieving insight. Almost the whole series had been treated by relatively inexperienced psychotherapists, but a slightly higher percentage of patients who showed improvement had been treated by the more experienced psychiatrists.

The scope of the study was limited by the type and amount of information available in the case records, but the authors' findings were consistent with theoretical concepts. It was suggested that further progress in solving the problem awaits more detailed investigations and methodological advances in analysis of the data.

DISCUSSION

DR. AUGUSTUS S. ROSE stressed the difficulties in all efforts at accurate evaluation of psychotherapy. He was impressed by the impersonal methods used by the authors.

DR. DONALD J. MACPHERSON expressed the opinion that psychotherapy itself needed defining. It is by no means a standard procedure. The intellectual level of the patient is of great importance in relation to the results achieved by any particular method.

DR. RUPERT A. CHITTICK asked whether the more successfully treated patients were exposed to a longer period of therapy.

DR. WILLIAM L. HOLT asked a number of questions bearing on the duration of hospitalization necessary to receive insight, as compared with the simpler forms of catharsis.

DR. HENRY H. W. MILES: I agree with Dr. MacPherson that the definition of the term "psychotherapy" is extremely difficult, especially in the context of this particular group of patients; our data were not detailed enough to give a clear picture of the therapeutic process. I agree with him that very often therapy is an educational process. It seems to be a matter of learning and development rather than of treatment in the medical or surgical sense. We did ask the patients for their own veiws of what had helped them. It was sometimes disappointing to find out what they thought. One young man who had shown remarkable improvement said: "Talking about things helped me. Bringing them out like they do here on the ward—that helped quite a bit." He also put weight on his realization that other people had the same sort of illness. His doctor would discuss with him the situations in which his symptoms developed. However, he said, he never learned why he had them. We formulated his "recovery" from the dynamic standpoint as follows: He had been quite well until he got into the Merchant Marine. After the stress of air raids and torpedo attacks, he exhibited anxiety symptoms. There was also much conflict over latent homosexuality. He had an intense attachment to an older man on board ship. That relationship seemed to be related almost as much to his anxiety as the bombings. When he got out of actual danger and into a protected environment, he improved rapidly. On leaving the hospital, he became a masseur and rubbed down athletes, an activity which seemed to be a socially acceptable sublimation of his unconscious homosexual trends.

An adolescent boy who had looked almost like a schizophrenic had remained a clinical "recovery" for about 10 yr. He said that "talking to the doctor" had not helped at all. The reason he gave for his improvement was that he was able to rest in the hospital and get away from his psychotic mother. We believed that his formulation was right. When the home situation had been improved by the commitment of his mother to a state hospital, and after a summer at camp, where he made friends, the patient felt fine. There was no actual working through of his problems in psychotherapy.

In answer to Dr. Chittick's question, I do not think that psychotherapy had much to do with the subsequent progress of these patients. It seemed to us, in considering the various factors, that the sort of environments the patient came from, the family situation, the life stresses he was subjected to, etc., were actually more important than the therapy in influencing the course of the neurosis. In many cases the warm relationship with the doctor was enough to

make the patient feel better, without development of insight or real understanding of his problems. The time element did not seem to be important. Of the patients who were unequivocally improved, those exposed to the longest treatment were not the ones who did best. The patients who did best had less treatment. The group which showed no improvement had relatively short treatment, but this seemed to be influenced by the quickly formed opinion that because of low intelligence quotients, language difficulty, etc., the patients would not be amenable to psychotherapy, and thus they were kept in the hospital only for brief supportive therapy or reassurance. Whether they would have improved had they stayed longer is hard to say.

Dr. Holt asked about length of hospitalization of the patients who had so-called insight-therapy as compared with that of patients who had simpler forms of therapy. When the patients were divided on this basis, the former group had a mean of 47 therapeutic hours, whereas the latter had only 24. In this group, with "therapy" we could not say that insight-therapy, defined in the sense of the treatment attempted, was better than other forms.

In regard to the lack of improvement in sexual adjustment, we felt that the symptoms of maladjustment, such as frigidity, impotence, or premature ejaculations were indicative of conflicts at a "deeper" level in the dynamic sense than were the overt anxiety symptoms, and thus were not really touched by the sort of treatment most of these patients received.

As to the relation of degree of improvement to length of the follow-up interval, there was no significant difference between patients who were much improved and those who had not improved at all.

Suppression of the Clonic Phase in Electrically Induced Convulsions in Man. Dr. Leo Alexander.

Electrically induced convulsions in man lasted an average of 50 seconds, including the latency period, as measured in 81 subjects by kymograph recordings, irrespective of the strength and duration of the convulsion-inducing stimulus.

Electrically induced convulsions can be made purely tonic instead of tonic-clonic, as they usually are, by continuing the stimulus which induced the convulsion through its entire duration. This observation lends support to Penfield's and Erickson's theory of the cortical origin of the clonic phase, for the clonic phase can be suppressed by a stimulus which must be presumed to have become inhibitory after its original excitatory effect.

As a practical measure, the use of this technique of suppressing the clonic phase has proved useful in preventing posticta1 respiratory embarrassment, and in my clinical work it has replaced the use of curare in administering electric shock to patients with abnormalities of the skeletal system, especially spinal fractures, to pregnant women, and to patients with other conditions in which violent clonic convulsions could be harmful.

DISCUSSION

Dr. William L. Holt asked whether suppression of apnea was of value as compared with the longer duration of the total fit. He found that though complaint of pain was less frequent after use of the Reiter machine, routine roentgenograms disclosed a similar incidence of fractures.

Dr. Martha Brunner-Orne reported good results with suppression of the clonic phase. She expressed the belief that fractures were produced by the initial jolt. The duration and type of fit appeared to be specific for each patient and were maintained in subsequent seizures.

Dr. D. Denny-Brown discussed the period of apnea in relation to the respiratory effects produced by focal stimulation of the frontal cortex. Such respiratory effects were closely allied to suppressor mechanisms, and strong stimulation produced rebound after-excitation in both these. This appeared to be the physiological explanation for the lessening of both clonus and apnea in weak stimulation.

Dr. Wilfred Bloomberg asked whether apnea resulted from overbreathing.

Dr. Leo Alexander: The intensity of current necessary to suppress the clonus during the seizure is the same as, or slightly less than, that necessary to produce the seizure. Lowering of the current by as little as one-eighth of the amperage usually will allow the clonus to break through to a slight degree, while with one-fourth to one-half of the current clonus will break through fully.

As to Dr. Holt's question concerning the value of the suppression of the clonic phase, I should like to make several comments. Quite apart from any statistics concerning apnea and fractures, it is obvious to anyone who witnesses the two kinds of treatment that the controlled tonic convulsion is a much gentler procedure. The patient lies quietly in tonic extension; the face is flushed, and respiration begins instantly at the termination of the seizure, or, if higher currents are used, can be brought back quickly by shifting to low voltage, nonconvulsive stimulation without turning off the current.

As to the more specific aspects of greater safety, there is no doubt that the method is capable of preventing postictal respiratory embarrassment and that after 460 consecutive treatments on 80 consecutive patients it has completely eliminated complaints referable to the spine. I have not routinely taken roentgenograms at the completion of such electroshock series. In two cases with old spinal fractures, however, roentgenograms were taken both before and after the series of controlled tonic electroshock treatments. The roentgenograms taken at the termination of this treatment series showed neither aggravation of the old fracture nor a new one. One cannot, of course, exclude the fact that in other cases asymptomatic fractures may have occurred.

I fully agree with Dr. Holt and Dr. Brunner-Orne that fractures may occur in any phase of treatment, particularly during the initial tetanic contraction, which should always be softened according to the glissando technique pioneered by Dr. Tietz.

That abolition of the clonic phase in no way lessened the antidepressant effect of electroshock treatment clearly indicates that the clonic phase is not necessary for the specific antidepressant therapeutic effect of electric shock.

The effect of prolonged stimuli, such as I have used, is more purely excitatory in all respects, as exemplified by the purely tonic nature of the contraction, the prevention of postshock apnea, and the lessening of subsequent memory disturbance.

I use the term "latency" for the tetanic contractions with rapid tremor, preceding the beginning of the tonic phase, because the contractions are due to the direct stimulation of the brain prior to reaching the convulsive threshold. During the phase of irregular tetanic activity with tremor, the subject is not yet irrevocably committed to the convulsion. Termination of the stimulus during the convulsion itself would not terminate the convulsion, but the convulsion would go on through its tonic and clonic phases, their duration in no way being influenced by the cessation of the stimulus. I felt therefore that it would be useful for a study of this type to differentiate between the build-up period, during which the subject is not yet committed to the total march of events characteristic of the convulsion, on the one hand, and the convulsion itself, during which the subject is committed to a definite march of events, on the other. I therefore called the former phase "latency"; the latter, the convulsion itself, I divided into its tonic and its clonic phase. This differentiation aided the clarification of the phenomenon under investigation, especially since the latency phase varied greatly with the amount and duration of the stimuli, whereas the convulsion itself showed little variation, except, of course, for the fact that the clonic phase could be reduced and the tonic phase relatively lengthened by the use of prolonged stimuli.

Dr. Bloomberg brings up an interesting point, suggesting that the apnea following the full seizure may be due to hyperventilation during the clonic phase. However, an important point against his explanation, and in favor of the assumption of cortical inhibition, is the fact that the patient is deeply cyanotic during this apneic phase following standard electroshock.

D. Denny-Brown, M.D., *Presiding*

Regular Meeting, Dec. 7, 1950

CLINICAL MEETING AT MASSACHUSETTS GENERAL HOSPITAL: REPORT OF NINE CASES

Bilateral Partial Thenar Atrophy. DR. JAMES B. AYER.

A housewife and stitcher, aged 54, in good general health, presented atrophy of the right thenar eminence of the "shelf," or "stepladder," type. Weakness was confined to the opponens pollicis and abductor pollicis brevis muscles. No muscular fibrillation had been observed by the patient or seen by the examiner. On two examinations no sensory abnormality was observed, except that slight tenderness was noted on pressure just above the transverse carpal ligament

in the midline. The patient stated that this condition commenced eight years ago, when she experienced severe pain in the thumb and adjacent two fingers, lasting two months, followed by progressive weakness and wasting. There had been no increase in disability for several years and no return of pain, but some paresthesia.

On the present admission, the patient said that the left hand had begun to show weakness of the same type two months before, and examination revealed opposition and abduction of the thumb to be weakened on the left side also, with minimal atrophy. There was no history of trauma to the wrist, neck, or elbow, and roentgenologic examination failed to show any pathological change in the cervical portion of the spine, shoulder, elbow, or wrist, and no cervical rib.

Comment.—This type of partial thenar weakness and atrophy, usually bilateral, and most frequently seen in women in the fourth or fifth decade of life, is now recognized as a clinical entity. It was described in 1909 and 1911 by J. Ramsey Hunt (*Am. J. M. Sc.* **141**:224, 1911) and attributed to pressure of the terminal motor nerves in the palm against the lower border of the carpal ligament. He emphasized the absence of sensory symptoms in his cases as indicating a pure motor disability. In subsequently published cases, we find some reports similar to his, but many others in which pain and paresthesias were early or persistent symptoms, and in these we must infer, from operative results, that the site of injury is within the carpal (flexor) tunnel.

In the earlier cases treatment was by long rest and fixation of the wrist, sometimes with success. Recently, prompt and very satisfactory results from section of the transverse carpal ligament have been reported. The findings and theories of causation are not always the same, but "neuritis from pressure" is the usual diagnosis (Cannon, B. W., and Love, G.: *Surgery* **20**:210, 1946. Brain, W. R.; Wright, A. D., and Wilkinson, M.: *Lancet* **1**:277, 1947. Kendall, D.: *Brain* **73**:84, 1950).

It should be emphasized that the case here discussed is one of a group of similar cases of an atrophy of insidious origin, bilateral in distribution, without associated evidence of trauma. One is strongly tempted to assume the presence of neuritis, probably due to repetitive pressure from occupation. One must not forget, however, that at least two authors believe that abiotrophy plays a major role in the phylogenetically late innervation of the thumb, as concluded by Brouwer (*J. Nerv. & Ment. Dis.* **51**:113, 1920) and Wartenberg (Partial Thenar Atrophy, ARCH. NEUROL. & PSYCHIAT. **42**:373 [Sept.] 1939).

DISCUSSION

DR. BERTRAM SELVERSTONE: Bilateral thenar atrophy is a rare condition. I saw 2,000 cases of peripheral nerve injuries during the war and operated in 700. In only two was this condition present. We did not decide about the cause. We sectioned the transverse carpal ligament, with good results. In both we thought the median nerve was somewhat swollen and red.

DR. JAMES C. WHITE: I have had two nontraumatic and three traumatic cases. Operative results have been good.

DR. D. DENNY-BROWN: I have seen several cases of this condition, especially in neurological outpatient clinics and in working-women past middle age. Tingling and paresthesias are commonly severe, without much sensory loss. It seems possible that periarticular thickening may encroach upon the carpal tunnel in persons of this age group, for arthritis in the hand is associated.

Orbital Gyrectomy for Intractable Pain. DR. F. J. BONNER, DR. STANLEY COBB, and DR. W. H. SWEET.

J. T., a man aged 65, was admitted to the hospital on May 15, 1950, because of severe burning pain of the left eye and supraorbital region acompanied with twinges of sharp pain on the left side. Six years prior to the present admission there had been onset of herpes zoster, involving the ophthalmic division of the trigeminal nerve. This was treated with local applications and eye drops. The swelling noted with the original lesion gradually subsided during the following year, but the burning pain in the left frontal-parietal area and in the left eyelid became more intense. Beginning one and one-half years after the onset of the pain and continuing to the

present hospitalization, numerous procedures had been carried out, in an attempt to relieve the pain. These included, in order, avulsion of the left supraorbital nerve; irradiation of the left trigeminal ganglion; left total retrogasserian neurectomy; left supraorbital gyrectomy, and resection of the superior cervical portion of the left sympathetic chain. All these procedures except the last two were followed by complete or marked relief of the pain for four to 12 days. After the left supraorbital gyrectomy, the patient was noted to have been very apathetic, spending most of his time sitting around the house with his eyes closed, and showing no interest in other members of the family, friends, or relatives or in the details of his personal appearance. These periods of inactivity and apathy were interrupted by daily periods of extreme restlessness, in which he would pace up and down the room nervously. Although he complained less of pain than prior to operation, when asked he stated that it was "just the same, if not worse." Three months after gyrectomy, he was admitted to the psychiatric service for observation; coincident with this admission there were a decrease in apathy and an increase in interest in those around him. At the time of his admission for a right supraorbital gyrectomy, two and one-half years after that on the left, the patient was noted to be alert and cooperative but spent a great deal of his time in the ward, as he had at home, sitting with his eyes closed. He would participate to a limited degree in ward activities, such as card games and occupational therapy, at which times he would open his eyes. He noted that the pain was constantly present and that the only relief he received was in sleep. Examination and laboratory studies gave results consistent with those expected from previous operations. On June 20, 1950, a right supraorbital gyrectomy was performed. Apathy was noted only during the first three or four postoperative days. Immediately after operation the patient noted that the pain had been relieved, and during the subsequent hospitalization, which extended over a period of about three months because of a complicating infection of the operative wound, the patient noted that his condition was constantly improving. When seen for evaluation of his status five months after operation, he was entirely free of pain except for very slight soreness of the eye. Since discharge he had been very active at home, doing carpentry for the neighbors and spending the remainder of his time in his workshop in the basement. He no longer found it necessary to keep his left eye closed. During the follow-up study he was sociable and cooperative.

DISCUSSION

DR. JAMES C. WHITE: I first tried cutting only the lower frontal connections, but 10 of the patients had such persistent apathy that I did not do it again. We performed this operation on patients who had only a short time to live; seven of them did well. I think that orbital gyrectomy will be the operation to use.

DR. D. DENNY-BROWN: What does this patient say about his pain now?

DR. STANLEY COBB: He says that it is gone.

DR. D. DENNY-BROWN: Do you think it is because his pain mechanism is destroyed, or because postherpetic pain may disappear spontaneously after several years?

DR. STANLEY COBB: It is now about five years since the operation. The pain began to subside after the first gyrectomy; if you asked him about it then, he would say he had pain, but he did not talk about it all day long. After the second gyrectomy he stated that he no longer really had pain. The pain subsided about six weeks after the last operation. He said the pain was all gone.

DR. W. H. SWEET: I heard a report at the Cushing Society from which I gathered that postherpetic pain is not likely to subside spontaneously.

DR. D. DENNY-BROWN: Postherpetic neuralgia is notoriously troublesome and may go on for years, and then disappear. If the patient admitted some pain or hyperesthesia, but was no longer preoccupied with it, I should feel more convinced about the part played by the gyrectomy.

DR. BERTRAM SELVERSTONE: How many neurologists have seen a patient with severe postherpetic neuralgia have a complete remission after three years?

DR. AUGUSTUS S. ROSE: I have seen one case.

DR. WILLIAM N. HUGHES, Providence, R. I.: Yes, but after two years of pain.

Calcification of the Carotid Sheath. Dr. Augustus S. Rose.

A. P., aged 36, a salesman, had right spastic hemiparesis and an irregular, hard, calcified (as seen in roentgenogram) mass in the left side of the neck. On March 15, 1942, he had sudden, sharp, generalized headache; dizziness; vomiting; disturbed speech, and, after a few minutes, loss of consciousness. When seen by a physician two hours later, he was drowsy, had a stiff neck and complete right hemiplegia. Two days later, he was responsive but aphasic, had a stiff neck, right hemiplegia, right hemianalgesia, a bilateral Babinski sign and 1 to 2 D. of papilledema. Lumbar puncture showed grossly bloody cerebrospinal fluid, with an initial pressure of 200 mm. and xanthochromia and a total-protein content of 308 mg. per 100 cc. The Hinton test of the blood gave a negative reaction. The patient was in bed six weeks. The speech disorder and hemiplegia showed gradual improvement. One year later, and for about one year thereafter, he had a series of fairly frequent Jacksonian seizures involving the right hand and arm, occasionally with loss of consciousness and generalized muscular activity. In the five years prior to admission he had had rare seizures. He was taking diphenylhydantoin, 0.2 gm., and phenobarbital, 30 mg., daily, but irregularly. In November, 1947, a painless swelling was noted on the left side of the neck. A roentgenogram showed calcification consistent with calcified hemorrhage, extending downward from the base of the skull into the upper part of the chest, following the course of the carotid sheath. No appreciable change in the amount or density of the mass was demonstrated in June, 1948, or on Nov. 29, 1950. Roentgenograms of the skull showed no change.

Comment.—This case, presented as showing an unusual complication of spontaneous subarachnoid hemorrhage, suggests that arterial rupture must have occurred at or near the place where the carotid artery leaves the dura mater, permitting the blood to extend in both directions. Calcification surrounding the artery may have reduced the patency of the lumen and served as a naturally occurring ligation.

DISCUSSION

Dr. William N. Hughes: If the hemorrhage is calcified, the blood must have been there at that time in substantial quantity.

Dr. D. Denny-Brown: The vessel does not feel tortuous, not like calcified degeneration of the artery itself. It does suggest calcification distending the sheath of the carotid artery. The absence of Horner's syndrome is remarkable.

Effects of Apomorphine and of Epinephrine on the Tremor of Parkinson's Disease. Dr. Robert S. Schwab.

Despite 125 years of therapeutic investigation, the results of efforts to eliminate the symptoms of Parkinson's disease have been universally disappointing. Only a return to 25 to 35% of the normal healthy state has been achieved by the many medical and surgical techniques in use. McColluch and Lettvin, at the University of Illinois, recently found that subemetic doses of apomorphine hydrochloride relieved considerably both the rigidity and the tremor. Dr. Henry Barcroft, of London, found that epinephrine in normal persons sometimes produces tremor. My colleagues and I were fortunate in having Dr. Barcroft with us recently and are now collaborating with him in following the blood pressure, pulse and tremor in a group of patients under the influence of each of these drugs.

The preliminary results follow.

1. Apomorphine reduces the blood pressure and also reduces both rigidity and tremor. Near-syncope reduced only the blood pressure. Lying-down minimizes the fall in blood pressure, and atropine eliminates the nausea, leaving only the improved clinical state.

2. Epinephrine increases the tremor considerably as the blood pressure rises. The effect seems to be eliminated in the presence of such drugs as trihexyphenidyl (artane®) and caramiphen hydrochloride (panparnit®).

An illustrative case was presented. A man aged 74, a retired electrician, first noticed tremor of the left hand eight years prior to admission. There was gradual progression of tremor with involvement of the right side—manifest as slowness in movement and stiffness of the limbs. The blood pressure was 145/90. He had been treated with trihexyphenidyl and diphenhydramine (benadryl®) during the preceding nine months, on which therapy he did fairly well. The patient

responded to intravenous administration of epinephrine hydrochloride with a rise in blood pressure to 175 mm. and an increase in tremor of about 35%. He responded to subcutaneous injection of apomorphine hydrochloride (with 0.3 mg. of atropine) with a fall in blood pressure of 20 points and a reduction in tremor of 50%.

DISCUSSION

The patient was presented before and after receiving a dose of apomorphine. The effect was somewhat disappointing.

DR. JOSEPH M. FOLEY: Did you give an emetic dose?

DR. ROBERT SCHWAB: No. The nausea can be eliminated by adding 0.3 mg. of atropine. If the patient is lying down, he does not have any discomfort except for drowsiness.

Falsetto Speech. DR. EDWIN M. COLE.

J. T., a youth aged 19, came to the nose-and-throat clinic in February, 1950, complaining of failure of his voice to change. He stated that for the past five years his voice had been very high-pitched and seemed to be getting higher. He was troubled with sore throat two or three times a week. He did not complain of dysphasia. Laryngoscopic examination revealed that the vocal cords moved well, although they seemed slightly thickened. There was a minimal amount of hypertrophy of the mucous membrane on the posterior third of the cords. The patient was referred to the language clinic. Neurological examination showed a physiological condition, with no abnormalities which could in any way account for the falsetto voice.

As indicated, the patient spoke in a high falsetto voice. With considerable encouragement and a few relaxation exercises, he was able to produce an excellent bass tone. The problem was explained to him as one of habitual misuse of voice, and arrangements were made for him to have intensive speech therapy. The patient made a rapid adjustment to his improvement in voice and has had no further speech difficulty.

DISCUSSION

The patient demonstrated his normal voice and the manner in which he spoke before treatment. Dr. Cole said that reeducation therapy had been given three times a week for two weeks.

Presentation of Two Patients with Myositis: Report on Muscle Biopsies. DR. E. P. RICHARDSON JR. and DR. VINCENT P. PERLO.

CASE 1.—L. M., a white woman aged 34, came to the hospital complaining of progressive weakness of the arms and legs of three-years' duration.

Three years prior to admission the patient noted weakness of the legs on climbing stairs and, shortly afterward, weakness of the arms and shoulders. Weakness had slowly progressed, without any associated sensory symptoms. There was no dysphagia or dysarthria. For about three years the patient had complained of sensitivity of her hands and feet on exposure to cold.

Thyroidectomy was performed at the age of 21. The family history was noncontributory. The patient was married and had three children, who were living and well.

Neurological examination showed generalized muscular weakness, most pronounced in the proximal muscles of all four limbs; moderate wasting of the muscles of the shoulder girdle and thigh, with no fasciculations; normal sensation; normally active arm and knee jerks; sluggish ankle jerks; normal plantar reflexes, and cyanosis of the fingers on exposure to cold.

Laboratory studies revealed creatine excretion, 0.35 gm. per 100 cc. (normal less than 0.1 gm); creatinine excretion, 0.50 gm. per 100 cc. (normal 0.75 to 1.25 gm.); spinal fluid, no cells and 38 mg. of total protein per 100 cc.; Wassermann reaction, negative; electromyogram, normal; protein-bound iodine, 7.6 γ per 100 cc. Biopsy of the right quadriceps gave a diagnosis of myositis.

CASE 2.—L. S., a white woman aged 46, came to the hospital complaining of generalized weakness for two and one-half years.

Two and one-half years prior to the present admission the patient noted weakness of her arms and soon afterward complained of weakness of both legs. Within several months she was unable to climb stairs and had difficulty in raising her arms. The weakness gradually pro-

gressed, and at the time of examination the patient was unable to walk or stand without support. There were no sensory symptoms, dysphagia or dysarthria. Four years prior to admission the patient first noted pain and cyanosis of her finger tips on exposure to cold.

Neurological examination showed myopathic facies; generalized muscular weakness, most pronounced in the muscles of the neck, shoulder girdle and hip; symmetrical atrophy of the involved muscle groups; no sensory loss; hypoactive deep reflexes; reflexes of plantar flexor type; absence of fasciculations; cyanosis of the fingers on exposure to cold.

Laboratory studies revealed creatine excretion, 0.43 gm., and creatinine excretion, 0.6 gm., per 100 cc.; electromyogram, normal; basal metabolic rate, —4%, and sedimentation rate, 1.59 mm. in one minute. Biopsy of the left deltoid and left quadriceps gave a diagnosis of myositis. (Biopsy sections from the muscles of these two patients were presented.)

DISCUSSION

Dr. Joseph M. Foley: Were either of these women at the menopause?

Dr. E. P. Richardson Jr.: No.

Dr. D. Denny-Brown: The patient was adipose; yet she had lost all the subcutaneous fat around the shoulders. Was there evidence of scleroderma?

Dr. Joseph M. Foley: These Raynaud-like changes may go on and present a picture of scleroderma.

Dr. Charles S. Kubik: In these cases there were signs of disorder of the vasomotor system before weakness appeared.

Dr. D. Denny-Brown: There is a chronic stage of this process which seems to me to be identical with the condition called thyroid myopathy.

Dr. E. P. Richardson Jr.: We have found no abnormality of the thyroid function.

Dr. Charles S. Kubik: Some of our patients with myositis have had joint pain and have also had something resembling rheumatoid arthritis. The absence of biopsy evidence does not rule out myositis. In differentiating it from dystrophy, the age of the patient is important. The course is more rapidly progressive in myositis.

Large Chordoma of the Left Temporal Area, with Surgical Removal. Dr. W. H. Sweet.

H. S., a man, aged 40, had been well until about five weeks before his admission, when he noted the gradual development of drooping of the left eyelid. There was diplopia on conjugate upward gaze, but not on downward gaze. About two weeks before admission, he noticed numbness of the upper part of his face, forehead and scalp on the left and decreased sensitivity of the cornea on that side. About one week before admission he noted decreased vision in the left eye and decreased strength in his right hand, manifested as inability to grasp objects as strongly as before. He admitted having headaches, primarily in the retro-orbital region bilaterally and spreading to the left temporoparietal region.

Neurological Examination.—There were marked lability of emotion and inappropriateness of thought content. Visual acuity was 18/20 in the right eye and 3/1000 in the left. There were present a partial defect in the right temporal field of the right eye, paralysis of the left third and fourth nerves and paresis of the left sixth nerve. The left pupil was 1.5 mm. larger than the right and did not react to light or in accommodation, neither direct or consensually. There was left exophoria of about 20 degrees. The eye was fixed except for slight ability to abduct; corneal sensitivity was absent on the left. There were hypesthesia and hypalgesia over the first and second sensory divisions of the fifth nerve and ptosis of the left lid, with complete closure of the eye. The right arm in extension showed motor weakness, with abduction of the fingers and flexion of the phalanges. Otherwise the neurological state was normal.

Hospital Course.—Examination of the patient in consultation with an otolaryngologist revealed nothing abnormal. A ventriculogram on Aug. 3, 1950, revealed a marked shift of the third ventricle to the right and elevation of the anterior portion of the left temporal horn. A chordoma lying medioventral to the left temporal lobe and ventral to the diencephalon and midbrain was removed. It had extended along much of the petrous portion of the left temporal bone. On the first postoperative day the patient was, against advice, up and about, asking to

go home. Postoperatively there were analgesia of the left side of the forehead to pinprick and absence of the corneal reflex on the left. The left pupil was 0.5 mm. greater in diameter than the right and did not react directly to light. There was no weakness of the face or upper limb. On the third postoperative day the temperature rose to 104.6 F. Lethargy was markedly increased, but there was equal strength and no pathological reflexes. At the height of this episode a ventricular tap showed an initial pressure of 160 mm.; the fluid was slightly pinkish-yellow and opalescent, with 8,250 red blood cells and 320 white cells, per cubic millimeter, and 81% polymorphonuclear leukocytes. Lumbar puncture at the same time yielded fluid of a similar appearance, with a red blood cell count of 5,000 and a white cell count of 220, per cubic millimeter, and 81% polymorphonuclear leukocytes. This decline, however, was followed by improvement. By the sixth postoperative day the patient was ambulatory and eating well.

Neurological examination at the time of his discharge, on the 18th postoperative day, showed the following abnormalities: visual acuity of 20/100 in the left eye; complete paralysis of the third, fourth, and sixth nerves on the left, with absence of the reflex to light and in accommodation, both direct and consensual; complete ptosis of the left lid, and absence of the corneal reflex on the left. The jaw deviated to the left on opening. There was a questionable paresis of the left side of the face, and the sensory disturbances were limited to the first and second divisions of the fifth cranial nerve. A postoperative electroencephalogram was interpreted as being a mildly abnormal record, and postoperative reontgenograms of the skull showed absence of the thinning of the floor of the middle cranial fossa noted previously. A postoperative test of cortical function revealed dull-normal general mental ability with slightly improved ability to learn new material. No evidence of aphasia was present.

Craniopharyngioma: Hormonal Changes Following Removal. DR. BERTRAM SELVERSTONE.

J. F., a girl aged 12 years, entered the hospital on Oct. 24, 1950, with complaints of retarded growth and epileptic seizures. She was born normally at full term. Her development in infancy was normal, but, although she seemed to progress mentally, her physical growth had not kept pace with that of other children of her age. During the past six years she had had seizures consisting of an "absence" of about three-seconds' duration, preceded sometimes by a sense of fear but without aftermath. At the age of 3 yr. convergent strabismus was noted on the right, and her parents were informed that "the nerve was dead." She is said to have been blind in the right eye at that time.

At operation, on November 15, a bifrontal exposure was made; the frontal lobes were separated after division of the falx, and the bony, hard tumor was identified within the sella, extending upward and indenting the medial surface of both frontal lobes. Seven cubic centimeters of yellow fluid was aspirated from within the tumor capsule. A large window was made in the intrasellar portion. The pathological diagnosis was craniopharyngioma (adamantinoma). The patient was treated with pituitary adrenocortotropic hormone (ACTH) before, during, and after operation and made an uneventful recovery. The chemical status was followed in detail and was described. Adrenal insufficiency did not, in fact, occur.

DISCUSSION

DR. STANLEY COBB: How much vision has she now?

DR. BERTRAM SELVERSTONE: Normal acuity, as before operation, and complete temporal hemianopsia, except for a little return in the lower temporal quadrant.

DR. OSKAR HIRSCH: This patient showed remarkably little discomfort three days after operation. I operated on one patient, 1½ yr. old, with such a cyst, by the nasal route. I drained the cyst and kept the drainage open with a tube. The child is doing very well.

DR. F. M. BLODGETT: We had evidence that this child had pituitary deficiency, but no indication of hypothyroidism or adrenal insufficiency. Under stress a deficient pituitary may prove inadequate to control the metabolism of salt, sugar, etc. Before operation we had this patient under treatment with ACTH, and during the operative course we kept careful charts of various functions, being ready to manage any deficiency. The patient did well, and I believe our technique is useful.

DR. BERTRAM SELVERSTONE: Dr. Blodgett and Dr. Talbott have followed four children in this way, and the results before, during, and after operation have been very good.

Autopsy Observations in a Case of Carbon Monoxide Poisoning. DR. RUTH E. STAUFFER.

A man aged 76 was found unconscious from carbon monoxide poisoning. His wife, later shown to have a carbon monoxide blood saturation of 55%, was found dead in the same room. The patient was immediately hospitalized, and at the time of admission he was comatose. There was inequality of the pupils; muscular tone was increased, as evidenced by increased resistance to passive movement; the tendon reflexes were brisk, and pathological plantar reflexes were not elicited. Within 27 hr. of admission, the patient became oriented and was able to give a history. A lumbar puncture performed on entrance revealed nothing abnormal. He was discharged, as improved, in nine days.

After discharge the patient was employed as a hotel handy man. About two weeks later his son found him lying in bed and unable to answer questions. The patient was admitted to a nursing-home, from which he was transferred to the hospital on the 37th day after exposure to carbon monoxide.

On his second admission to the hospital, he was stuporous and incontinent of urine and feces. There were generalized increase of muscular tone, brisk tendon reflexes and extensor plantar reflexes. The patient remained in a stuporous state, from which he could be aroused only by strong stimuli, but did not speak. After 19-days' observation, he was discharged again to a nursing-home. His condition was essentially unchanged from that on admission. Because of progressive deterioration, he was transferred five days later to the hospital for terminal care. The coma deepened; the muscular resistance increased, and respiratory difficulty developed. The patient died on the third hospital day, 64 days after asphyxiation.

Brain.—There was pronounced degeneration in the subcortical white matter, involving both the myelin and the axis-cylinders. This was not complete, and there was no definite evidence that one element was involved more than the other. The immediate subcortical fibers were relatively spared, and in most places the overlying cortex was preserved. There were very small cystic cavities in the globus pallidus on both sides.

DISCUSSION

DR. RAYMOND D. ADAMS: The lesions of the white matter are strange. Dr. Morrison demonstrated lesions in the white matter in the brains of monkeys he took up to high altitudes. The extensive lesions in the white matter, without the usual nerve-cell degeneration at the junction of cortex and white matter, particularly in the hippocampal region, are unlike either carbon monoxide poisoning or anoxia.

DR. CHARLES S. KUBIK: Late exacerbation of symptoms has not occurred in any case that I know of. Degeneration in the white matter has been usual in our material. Degeneration in the Purkinje cells is more unusual. No two cases are exactly alike. Perhaps the degree of asphyxia varies, as well as the survival time. There may also be a difference in the effects of a severe asphyxia of short duration and those of an asphyxia extending over a longer time.

D. Denny-Brown, M.D., *Presiding*

Regular Meeting, Jan. 19, 1951

Herniation Through the Incisura Tentorii: Its Diagnosis and Treatment in Cranio-cerebral Injuries. DR. DONALD MUNRO.

This paper is to be published elsewhere.

Surgical and Irradiation Treatment of Chromophobic Adenomas of the Pituitary: Relation of Type of Operation to Immediate and Five-Year Mortality Rates. DR. GILBERT HORRAX.

A series of 105 verified chromophobic adenomas of the anterior lobe of the pituitary which were treated between 1932 and 1949 was studied. Certain general indications for initial surgical

or radiation therapy were noted, and the early, as well as late, results of the transsphenoidal and the intracranial operation were compared. The immediate mortality after craniotomy is considerably higher than that following the transsphenoidal procedure, but the situation is reversed in respect to the five-year mortality rate from recurrence of growth. Large intracranial extensions outside the sella turcica are responsible for the additional risk with craniotomy, but it is only by taking this risk that anything could be accomplished for these extensive tumors. The end-results with respect to vision after surgical treatment alone, after surgical treatment plus irradiation, and after irradiation alone were given.

DISCUSSION

DR. OSKAR J. HIRSCH: I should like Dr. Horrax to explain what was meant by cerebral extension.

DR. GILBERT HORRAX: In the transfrontal operation, or craniotomy, a large number of the adenomas can be visualized. Some of them occupy the sella turcica; others extend into the temporal or the frontal lobe. In some instances I have had to do a second craniotomy to get the whole tumor. In the present series 29 tumors had such extensions.

DR. OSKAR J. HIRSCH: I have three methods for the treatment of tumors of the pituitary: X-irradiation, the transfrontal, and the transsphenoidal. Each method has its limitation. X-rays cannot be used for cystic tumors; the transsphenoidal method cannot be used for supradiaphragmatic tumors, and the transfrontal method (according to Henderson) has its contraindication in the cases of prefixed chiasm, homonymous hemianopsia and aged persons.

The choice of any surgical procedure should be based on the lowest risk and the longest-lasting cure. The mortality for the transsphenoidal method is 5%, due to meningitis, which is now curable with the antibiotics. As for the life expectancy, I am in touch with 19 of my patients who survived 19½ to 30 yr. and maintained, most of them fully, and a few to a less degree, the improved vision achieved by the operation and radium treatment.

Each of the three methods mentioned must be considered when the problem of the treatment of a pituitary tumor arises, and we must use them in cooperation for the best of our patients.

DR. CLEMENS E. BENDA: I should like to ask Dr. Horrax about the term "chromophobic tumors." I understand that he includes in this category all tumors which are not eosinophilic or basophilic. However, the chromophobic cells of the pituitary represent a large number of various types. I wonder whether any differentiation of the various chromophobic cell tumors has been made. One type, which really deserves the term "adenoma," develops always within the anterior lobe and never grows beyond the boundaries of the anterior lobe. This tumor does not cause any endocrine symptoms but produces symptoms of compression and may produce endocrine symptoms through the replacement of functional eosinophilic and basophilic cells. This "chromophobic tumor" is the one which is probably well approached by Dr. Hirsch's method, and the postoperative results may be good. Whether the cells are sensitive to X-radiation, I do not know.

Other types of chromophobic tumors are those which come from embryonic cells near Rathke's pouch; these cells frequently give rise to suprasellar tumors. They develop either above that tentorium of the pituitary, from the stalk, or grow inside the sella and above, producing large tumors, which frequently spread over the base of the skull.

Dr. Horrax's pictures suggest that some of the tumors he discussed were suprasellar tumors of the stalk and Rathke's pouch. I should like to ask whether any differentiation of the tumor types has been made, for I feel sure that the response to X-ray treatment differs according to the type of the chromophobic cell.

DR. RAYMOND D. ADAMS: Did the endocrine status of the surgical patients differ from that of patients treated with X-rays? The pituitary status might be different in the transsphenoidal operation.

DR. D. DENNY-BROWN: The poor prognosis in cases with large supradiaphragmatic extensions raises the question whether X-ray therapy alone is advisable in such cases. The aim of such therapy presumably is to cause necrosis in such extensions. Dr. Heusner has, however, reported the catastrophic effect of spontaneous necrosis of such intracranial extensions; perhaps he would comment on this aspect of the question.

DR. A. PRICE HEUSNER: In looking over pathological material with Dr. Raymond D. Adams and Dr. M. F. Brougham, we noted that a number of extrasellar extensions either into the posterior fossa or into a temporal lobe had undergone infarct necrosis, probably because growth had outrun blood supply and had produced clinical catastrophies. Therefore, if there were evidence of extrasellar extension, we would be loath to recommend X-ray therapy for fear that the swelling consequent on irradiation might precipitate necrosis of the extrasellar tumor and create a surgical emergency, from which few patients recover.

DR. GILBERT HORRAX: I am sure Dr. Hirsch understands my attitude in this manner. I have the highest regard for him and his early efforts in treatment of pituitary adenomas. I believe there is a place for these three methods, as he mentions. Personally, there is no place for a transsphenoidal approach in my practice. It is many years since I have done one. I can accomplish the same result by craniotomy, with a low mortality for the adenomas within the sella. The extensive tumors which could not be helped by the transsphenoidal approach would have to be done by that method anyway. This paper dealt entirely with what I call chromophobic adenomas. There is no way of knowing whether or not an adenoma is cystic before operation. If radiation is given a trial and the patient does not show much improvement, operation is indicated. I feel that Henderson's indications concerning prefixed and postfixed chiasm have been overemphasized. In patients having a homonymous hemianopsia there is evidence of a postchiasmal growth, and we have had to remove the tip of the frontal lobe. I have had a number of older patients, too, and some of them have had enormous intracranial extensions. If I could do the nasal operation as well as Dr. Hirsch, I should doubtless use it in selected cases.

The endocrine status was sometimes helped by operation. Sometimes it has been helped by hormonal therapy. Recently I have given pituitary adrenocorticotropic hormone to some of the patients with low basal metabolic rates, secondary anemia and fatigue, with considerable benefit.

I have hesitated to do air studies, except in rare instances, because it adds one more procedure. The patients are already poor operative risks. I have limited my X-ray treatments, which in many instances will not affect the extensive tumors. I shall probably get better results with a 2-million-volt machine.

A New Technique for Gradual Occlusion of the Carotid Artery. DR. BERTRAM SELVERSTONE and DR. JAMES C. WHITE.

Ligation of the internal carotid artery is a procedure of therapeutic or prophylactic value in certain cases of intracranial arterial aneurysm, arteriovenous fistula, or other major vascular malformations. Since a number of older patients will not tolerate such occlusion, we have devised an instrument which permits the gradual occlusion of the vessel over a period of several days by means of a stainless steel clamp, which may be left permanently in place when closed, and whose emerging stem can then be removed without the necessity of a second operation. Blood flow can be increased at any time should partial occlusion cease to be tolerated. This device has now been used in four cases. In three, cases of a subclinoid aneurysm of the internal carotid artery, a carotid-artery-cavernous-sinus fistula, and a massive, inoperable arteriovenous anomaly, respectively, gradual occlusion was carried out without incident. The emerging stem was then removed, leaving the clamp behind, and the wound in each instance healed *per primam intentionem*. Two of the patients had been unable to tolerate test occlusion of the internal carotid artery. A fourth patient, whose common carotid artery had been invaded by carcinoma of the larynx, failed to tolerate gradual occlusion and a propagating thrombus developed, with production of severe hemiparesis. In the three successful cases the clamp has been in place from one to nine months, without symptoms.

DISCUSSION

DR. JOSEPH M. FOLEY: What is the disadvantage of removing the clamp after complete occlusion has been obtained?

DR. BERTRAM SELVERSTONE: Merely that another operation is involved. We have been reluctant to reexpose and manipulate the artery more than is necessary because of the possibility that a small thrombus distal to the site of occlusion might be dislodged.

Use of Streptokinase and Streptodornase in Treatment of Chronic Subdural Hematoma. DR. HANNIBAL HAMLIN.

Streptokinase is a fibrinolysing catalytic enzyme, and streptodornase (desoxyribose nuclease) is a nucleoprotein-lysing enzyme derived from nonpathogenic streptococci. Tillett and Sherry (*J. Clin. Investigation* **28**:173, 1949) have demonstrated the clinical use of these substances, as derived in lyophilized form, in causing lysis of intrapleural blood clots and related coagulum of exudates. Sixty-thousand and 80,000 units of streptokinase and streptodornase, respectively, were injected into a large solid subdural hematoma in an elderly patient via burr holes, through which 80 cc. of blood had been evacuated 15 days previously. Craniotomy 16 hr. later revealed that the major portion of the hematoma had been changed to a soft, semiliquid consistency, nonadherent to the brain surface, which was easily removed without damage to cortical vessels. The exposed cortex appeared healthy and pulsating; reexpansion of the molded hemisphere apparently had been facilitated. The patient showed no evidence of any toxic reaction and made an excellent recovery.

Other possible uses for streptokinase and streptodornase in neurosurgery are in conjunction with antibiotics in treatment of brain abscess by serial tapping and, similarly, in the management of extradural and subdural empyema, and in promotion of lysis of fibroblastic exudates in the meningitides, notably influenzal and tuberculous meningitis.

Further trial of these enzymes in these conditions will result in development of better methods of administration and proper dosage.

DISCUSSION

DR. GILBERT HORRAX: Was there any effect of these substances on the membrane around the hematoma next the pia and dura?

DR. A. PRICE HEUSNER: What is known about the effects of these products on the subdural membrane itself and on the leptomeninges?

DR. HANNIBAL HAMLIN: In my case the subdural hematoma was not encapsulated by membrane. The outer surface of the clot was adherent to the dura, where fibroblastic invasion had occurred. The deeper layers over the intact arachnoidal surface of the brain were liquefied, and no membrane could be identified.

The preparation used in this instance contained 300,000 units of streptodornase and 200,000 units of streptokinase. The latter alone might be more effective than in combination.

These enzymes should be used only in selected cases of chronic subdural hematoma, such as the one described, until we are more familiar with their action on the brain. The intact pia-arachnoid probably is a better protective barrier against possible absorption of toxic factors than the pleural covering of the lung. If contused and lacerated brain tissue were exposed directly to the streptokinase-streptodornase solution there might be unforeseen complications of systemic nature from absorption, rather than from destruction of viable brain tissue. The action of theses enzymes may be different in the subarachnoid than in the subdural space. Many other questions are posed by possible neurosurgical applications of streptokinase and streptodornase.

PHILADELPHIA NEUROLOGICAL SOCIETY

Michael Scott, M.D., Presiding

Regular Meeting, Feb. 2, 1951

Brain Tumor in an Infant: An Unusual Case. DR. MICHAEL SCOTT, DR. FREDERICK MURTAGH, and DR. AUGUSTIN PEALE (by invitation).

An infant aged 8 mo. was admitted to the hospital in April, 1949, because of right hemiparesis, persistent vomiting and frequent petit-mal seizures. The initial clinical impression was that of a subdural hematoma on the left side, and subdural punctures yielded 15 cc. of xanthochromic fluid from that side. Pneumoencephalograms disclosed massive shifting of the ventricular system from left to right. Trephination failed to uncover a subdural hematoma or hygroma, but exploratory craniotomy, done because of the massive ventricular shift, exposed a large, firm tumor deep in the temporal lobe. This was removed in a two-stage operation. The

tissues presented many of the characteristics of a ganglioglioneuroma, but two well-known consultants called the tumor an astrocytoma Grade II. The child has maintained a satisfactory recovery, with minimal neurologic sequelae.

The authors emphasized the diagnostic limitations of subdural punctures. In this case the xanthrochromic fluid obtained from such a puncture suggested subdural hematoma or hygroma. The encephalogram, however, suggested a massive shift of the ventricular system, and when a subdural hematoma was not found at simple trephination, the authors were encouraged by the air studies to proceed with craniotomy, which disclosed the true nature of the lesion.

DISCUSSION

DR. EARL WALKER: This case illustrates how much can be accomplished in a situation which seems to offer little chance of success. I have removed a tumor from a child 6 mo. old and another from an infant between 2 and 3 wk. of age. The first case was similar to the present one in that subdural fluid was found and air studies were necessary to make the diagnosis. Dr. Harvey Cushing had several similar cases, in which there was survival for several years without recurrence. In one girl a paracentral tumor was removed successfully 15 yr. previously, the histological picture of which was similar to that in the case described here.

DR. HELENA RIGGS: I have seen a case of ganglioneuroma in a 7-yr.-old child who survived one and one-half yr. after operation.

DR. MICHAEL SCOTT: Our reason for going back a second time was that the tumor had seemed so hard and firm that we felt we had a chance of removing it completely. Furthermore, the unsuitability of this case for X-ray treatment gave us no alternative which might conceivably help the child.

Vertigo Due to, or Associated with, Exposure to Certain Toxic Agents, with Special Reference to DDT, Formaldehyde and Other Disinfecting Agents. DR. JOSEPH C. YASKIN, DR. CARL HOFFMAN, DR. HARRY SLADE (by invitation), and DR. ROBERT L. LEOPOLD (by invitation).

While it has long been known that vertigo may be due to exogenous toxic agents, it is becoming evident that in recent years such cases have increased in frequency, owing to the use of certain disinfectants, notably DDT (dichlorodiphenyltrichloroethane). The authors reported on three groups of cases, the vertigo in one being due to formaldehyde, in a second to DDT, and in a third to less clearly understood disinfectants. Three illustrative cases were given for each group. The diagnosis was based on the presence of vertigo and associated symptoms, notably tinnitus and deafness (usually unilateral), nausea, and vomiting. In each of the cases there were a clear history of exposure, absence of structural disease of the nervous system, and, in the majority of cases, auditory disturbances. Results of Bárány studies were suggestive of the implication of the labyrinth but not of the central nervous system. In each case, removal of the agent was followed by recovery and arrest of the auditory disturbances.

It was concluded that many cases of vertigo are due to known, and probably unknown, toxic factors. Attention was directed to the fact that with the advent of DDT this condition occurs with greater frequency, affecting predisposed persons. The need of one's being on the lookout for toxic factors in association with vertigo was stressed.

DISCUSSION

DR. BENJAMIN SCHUSTER (by invitation): I was particularly delighted by this paper because no mention was made of Ménière's disease. I believe that this term applies only to a group of symptoms the causes of which are many. The agents which the authors have mentioned are not widely reported as having produced vertigo. This report should stimulate us to search for other agents, instead simply of calling the disorder Ménière's disease. I should like to point out that the problem with streptomycin is somewhat different. This drug does not affect the labyrinth directly, and hearing is undisturbed. Work on animals at the University of Pennsylvania has shown that most degeneration following administration of streptomycin occurs in the vestibular nuclei and in the cerebellum, and not in the labyrinth.

DR. MICHAEL SCOTT: Were tests made for sensitivity to these substances? Was the possibility of arsenic considered in the cases among fruit growers? Where does dimenhydrinate (dramamine) act?

DR. JOSEPH YASKIN: Dr. Schuster and I have agreed that much is wrong in referring to these symptoms as Ménière's disease. We did not make tests for sensitivity in these cases but relied upon the therapeutic test of controlling exposure to the agents. There was no other evidence, such as neuritis, renal disease, or anemia, which would have pointed to arsenic as a cause in these cases. I am unable to answer the question about the action of dimenhydrinate.

DR. BENJAMIN SCHUSTER: When dimenhydrinate is given to animals, there is no reduction in vestibular function. It apparently acts on the connections between the vestibular nuclei and the sympathetic system and thereby relieves nausea and vomiting, but not vertigo. It should be pointed out that in the present cases nystagmus occurred during the acute phase but did not persist, as it does with an intracranial lesion.

Thrombosis of the Internal Carotid Artery. DR. HERBERT C. JOHNSON, Baltimore (by invitation) and DR. A. EARL WALKER.

The case histories of six patients with spontaneous thrombosis of the internal carotid artery were presented. In each instance the diagnosis was made by angiography. A total of 83 cases of thrombosis of the internal or the common carotid artery which was diagnosed by arteriography have been reported previously. A review of the symptomatology reveals that headache, hemiplegia, and aphasia are common. In about 40% of cases there are ocular symptoms. The illness may have a sudden catastrophic onset or a slowly progressive course, or it may be characterized by intermittent transient attacks. Various etiologic factors, such as intracranial aneurysm, arteriosclerosis, and thromboangiitis obliterans, were discussed.

In five of the cases reviewed the common, external, and internal carotid arteries were found to be thrombosed. In the remaining cases the thrombosis involved only the internal carotid artery, usually within several centimeters of the bifurcation of the carotid artery, although in several cases the site of occlusion was at the carotid sinus. In treatment, cervical sympathectomy and excision of a segment of the thrombosed vessel have been tried. The prognosis for improvement is not particularly hopeful. Only about 25% of patients show any improvement. Spontaneous thrombosis of the internal carotid artery is probably commoner than has been thought. While in some instances a tentative diagnosis can be made on the basis of ophthalmological findings, many of the patients are suspected of having a brain tumor or an aneurysm. In this group of patients the diagnosis can be made with the use of arteriography.

DISCUSSION

DR. RUDOLPH JAEGER: I have seen six or seven patients who had occlusive thrombosis of the cervical portion of the internal carotid artery with severe neurological symptoms, headache and hemiparesis usually being prominent features. In four the thrombosis was noted on direct exposure of the carotid bifurcation when arteriography suggested or actually disclosed the nature of the lesion. Undoubtedly many persons have this lesion without symptoms that demand medical attention, since it is well known that the internal carotid artery can usually be ligated without symptoms of occlusion developing. A weak point in our understanding of this disorder is the ultimate prognosis for such a thrombosis. When it occurs in the relatively young, as it frequently does, without arteriosclerosis, the outlook should be good, but there is little evidence at present to substantiate such an opinion.

Dr. Walker's presentation has helped to clarify the nature of the disorder in cases with symptoms suggesting intracranial hemorrhage or neoplasm.

DR. ALEXANDER SILVERSTEIN: I have had under observation for several years a patient who has suffered in succession sudden blindness of the right eye, aphasia, and left hemiplegia. Air studies led to a diagnosis of encephalomalacia, but I am inclined to suspect that she may have had a thrombosis, such as the authors have discussed.

DR. HENRY SHENKIN: I can recall only one case in my experience in which this condition was demonstrated by angiography—that of a child 5 or 6 yr. of age who had a high fever and was shown to have had encephalitis, followed by hemiplegia. In this case the carotid pulse was

less palpable on the affected side. It would appear, therefore, that encephalitis should be included among the possible causes of this condition.

DR. WALTER SHEUERMAN (by invitation): Would it be possible to open the arteries in these cases and remove the thrombus?

DR. JOSEPH YASKIN: I have had three experiences with this condition. In the first case the thrombus followed a trauma, and Dr. Groff noted the cerebral softening at operation. The coroner found the thrombus. In the second case the cause was never discovered. In the third the condition developed after a conventional thyroidectomy, and right hemiplegia appeared five days after operation. Inspection of the wound revealed unusual swelling on the left side, and the surgeon removed 500 cc. of serous fluid.

DR. ROBERT GROFF: I have been impressed by the necessity of exploration in order that a certain diagnosis of this condition may be made. In some recent cases I have found congenital absence of the internal carotid artery, so that failure of the vessel to fill in an angiogram does not necessarily mean that there has been a thrombosis.

DR. MICHAEL SCOTT: Does Dr. Walker feel that angiography is dangerous in cases in which thrombosis is a possibility? It has been my experience in cases of thrombosis in other areas that this procedure leads to greater reactions.

DR. EARL WALKER: I agree that many patients with this condition may well be asymptomatic. I did not mean to imply that failure of the carotid artery to fill in the angiogram meant occlusion of the artery. Not only may the artery be absent congenitally, but technical difficulties sometimes lead to its failure to fill. It might be feasible to remove the clot from the vessel if the patient were seen a few hours after the thrombus formed. Usually the case does not come to our attention for weeks or months after thrombus formation, and by that time there is so much organization of the thrombus that removal is impossible. There is certainly some danger in angiography. In the present cases we did not suspect other vascular disease, and we had no complications. We have had difficulty with patients of a somewhat older age group, particularly those between 60 and 65.

Effects of Cortical Stimulation and Ablation on Experimental Hypertension in the Dog and Monkey. DR. HERBERT C. JOHNSON (by invitation) and DR. KENNETH M. BROWNE, Omaha.

A number of authors have reported autonomic responses following stimulation of various regions of the cortex in man and animals. The experiments described here were carried out in an attempt to study in animals with chronic hypertension the effects of ablation of those regions of the cortex which are known to give rise to elevations of blood pressure when stimulated. A number of dogs were made hypertensive by bilateral excision of the carotid sinus and aortic depressor nerves. After a period of observation of up to one year, stimulation of the orbital gyrus, cingular gyrus, and motor cortex resulted in the same changes in blood pressure as in the normal dog. Ablation of these regions of the cortex did not significantly alter the hypertension. A group of monkeys was made hypertensive by interference with the blood supply to the kidneys. Two animals showed a decrease in the severity of their hypertension following resection of the orbital gyri. The results obtained seem to indicate that excision of the cortical autonomic regions has little effect on the type of "neurogenic" hypertension produced in dogs.

DISCUSSION

DR. HENRY SHENKIN: I should be amazed if cortical ablation affected hypertension produced by removal of the carotid sinus. One might hope for better results when the hypertension developed on a psychogenic basis. I undertook to accomplish this some years ago, but the methods I used required so much time for establishment of the hypertension that the animals were not suitable for experimentation. I believe Dr. Gardner reported a case in which the cutting of the pituitary stalk led to reduction of hypertension in a patient for the six months he lived after the operation. I once carried out this procedure in a case of severe malignant hypertension in which the patient obviously was going to die. Unfortunately, the blood pressure dropped to normal levels, resulting in decreased function of the kidneys, so that she produced no urine during the postoperative period and died five days later.

Hugo Mella, M.D., *President, in the Chair*

Regular Meeting, Feb. 9, 1951

Organization and Administration of Neuropsychiatry in the Office of the Surgeon General II, 1948-1950. COLONEL JOHN CALDWELL, MEDICAL CORPS, ARMY OF THE UNITED STATES.

In the last few years the Army Medical Service has been faced with ever-increasing responsibilities, and these responsibilities have been notably increased since June 25, 1950, with the onset of hostilities in Korea. A flexible organizational structure for neuropsychiatric service in the Army has been largely completed by translating concepts evolved during World War II into firm Army doctrine and directives. The main problem before us at present is the procurement, training, and effective utilization of personnel. These points will be discussed briefly.

The Psychiatry and Neurology Consultants Division has the function of reporting to and advising the Surgeon General on all matters pertaining to psychiatry, neurology, mental hygiene, clinical psychology, and social work. In recent months there has been an increasing number of officers assigned to the Division, principally to deal with problems of psychology and social work. The duties of neuropsychiatric personnel in all echelons of Command and in medical installations have been established and described in appropriate Army directives. Methods of communication have been established from central points of authority to far-distant medical installations, enabling us to be at all times cognizant of prevailing conditions affecting mental health.

The military occupational specialists for neuropsychiatric personnel have been greatly increased, thus enabling a much firmer control of asssignment. A specific plan for the care of neuropsychiatric combat casualties has been established, employing the utilization of mobile psychiatric teams. The principles of combat psychiatry, treatment of combat casualties, and the legal aspects of psychiatry in military law are readily available in current Army publications.

Clinical psychology and psychiatric social work have been firmly established as a part of psychiatric services in the Army. The procurement of these allied specialists, as well as graduate training for psychiatrists and neurologists, has been proceeding satisfactorily.

Induction physical and mental standards for military personnel have been generally lowered to conform to the experience gained during World War II. The desirability of separation through administrative channels for those unable to serve by reason of unfitness or unsuitability has been emphasized.

Much more attention has been given to aspects of preventive psychiatry, with factors especially considered in relation to combat performance, environmental situations, classification and assignment, training system, replacement system, rotation system, personnel policies, leadership, unit and group identification, religious influences, orientation, attitudes, incentives, motivations, and education in mental health.

DISCUSSION

DR. M. M. PEARSON: I should like to ask, Colonel Caldwell, whether there is any provision for the matter of propaganda in your division.

DR. BALDWIN KEYES: I should like to express our appreciation of this optimistic picture of the new picture in the Army. By contrast, I might mention that about 1940 I happened to be in the Surgeon General's office. I walked into the psychiatrist's office and offered my services; but he answered, "We don't need a psychiatrist. We have one."

I was interested in the matter of communication. I think we are all aware that under the old system anything of scientific value would be lost in channels. This new system is a tremendous step forward.

Would Colonel Caldwell give us more information on the induction of men with neuropsychiatric disabilities through the induction boards?

COLONEL JOHN CALDWELL: First, in answer to the question of propaganda, there has been a division set up on a General Staff level—the Division of Psychological Warfare. Its purpose is to handle this whole area of information to our own forces and to other forces. This was

expanded recently to 25 officers. They are now recruiting more personnel. Do we have anything to do with it directly? No. Indirectly? Perhaps yes.

With regard to neuropsychiatric disabilities on induction: People have been brought in and then put out because there was no place to assign them. We lost 18,000 men last year who were separated because of unsuitability. No one would take the trouble to modify the training program or to see them through their difficulties. Then, too, we do have some difficulty in the matter of saying what is a neurosis. When is a man unsuitable, and when is a man sick? As you know, they once said that there should be no one in the Army with a diagnosis of neuropsychiatric disability. I notice they don't pay too much attention to the labels now.

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